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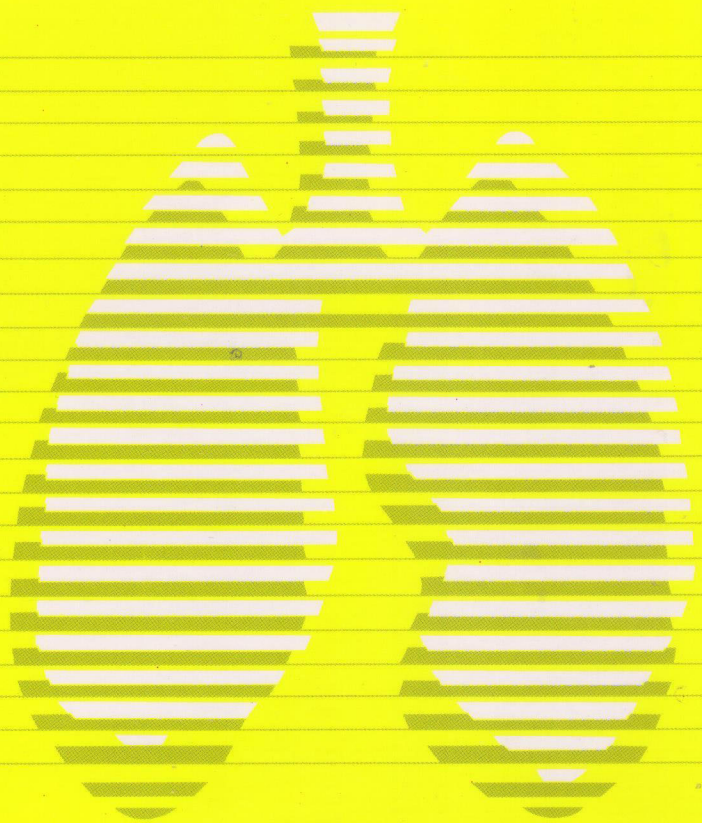

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原著

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Orginial Articles

Case Reports

Yawning as a Predictor of Survival in Critically Ill Mechanically Ventilated Patients

Hsiu-Nien Shen, Han-Siong Toh, Yu-Ju Ting*, Mei-Chen Chen*, Mei-Li Shen*, Chin-Li Lu**, Kuo-Chen Cheng

Objectives: Yawning can be used as a functioning index for the central dopaminergic system and is part of a neural network involved in empathy. The presence of yawning indicates intact functioning in these brain areas. Since encephalopathy occurs frequently in critically ill patients and is associated with patient outcome, we hypothesized that the presence of yawning, as a measure of brain function, might be associated with mortality in critically ill patients.

Material and Methods: A total of 99 consecutive patients who were admitted to a medical intensive care unit (ICU) at a tertiary-care hospital between July 1 and November 30, 2006 were prospectively investigated. The occurrence and frequency of yawning were recorded by ICU nursing staff. Multivariate logistic regression was used to determine the independent relationship between yawning and clinical outcomes.

Results: About 50% of patients, whether they received invasive mechanical ventilation (MV) or not, had yawned during their ICU stay. Patients who never yawned in the ICU tended to have non-neurological diagnoses (p=0.035) or shock (p=0.045), or used vasopressors (p=0.035), and were more seriously ill as measured by the APACHE II score (p=0.004), compared to those who had yawned during their ICU stay. In the logistic regression model, we found that only the presence of yawning (adjusted odds ratio [OR] 0.24, 95% CI 0.06-0.94, p=0.04) and use of vasopressors (adjusted OR 9.9, 95% CI 2.55-38.45, p=0.001) were independently associated with ICU mortality among MV patients.

Conclusions: Yawning is a relatively uncommon behavior in the medical ICU, and its occurrence in MV patients predicts a better survival. ***(Thorac Med 2009; 24: 1-10)***

Key words: yawning, mechanical ventilation, critical illness, prognosis

Introduction

Yawning, a phylogenetic behavior, and present in reptiles, birds and mammals, has been studied for several decades, but to date its physiological function is still unknown [1]. Yawning occurs frequently in daily life and is often attributed to boredom and fatigue [2]. Yawning can be used as a functioning index of the central dopaminergic system, including the nigrostriatal

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dopaminergic pathway, the paraventricular nucleus (PVN) of the hypothalamus and the pituitary gland [1, 3], and is part of a neural network involved in empathy, because it evokes unique neural activity in the posterior cingulate and precuneus, which play in self-processing [4]. The presence of yawning indicates intact function in these brain areas.

Due to complex neuropharmacological interactions [1], yawning is subject to the influences of aging [5], the sleep cycle [6], stressful situations [7], hypothalamus-pituitary-adrenal and sexual hormones [8-11], and medications with dopaminergic, cholinergic, adrenocorticotropic hormone (ACTH)-ergic and oxytocinergic activities [1, 12-13]. Rarely, excessive or pathological yawning may be a symptom of serious underlying medical illnesses [2], primarily involving the central nervous system, such as migraine, stroke, epilepsy, encephalitis, Parkinson's disease, hypophyseal tumors, psychiatric diseases, vasovagal syncope or cardiac tamponade [1-2, 12-13]. Since neurological and endocrine dysfunction occurs frequently in critically ill patients and is associated with patient outcome [14-15], there might be some change in this common, everyday behavior. Therefore, we hypothesized that the presence of yawning, as a measure of brain function, might be associated with outcome in critically ill patients. We carried out this study to understand the characteristics of yawning and to investigate its relationship to the outcome of critically ill patients in the medical intensive care unit (ICU).

Methods

Ninety-nine consecutive patients who were admitted to a medical ICU at a tertiary-care hospital between July 1 and November 30 in 2006 were prospectively investigated. Demographics, admission diagnosis, systemic inflammatory response syndrome (SIRS) score [16], Acute Physiology And Chronic Health Evaluation (APACHE) II score [17], Sequential Organ Failure Assessment (SOFA) score [18], simplified Therapeutic Intervention Scoring System (TISS) [19], uses of vasopressors, oxygen, artificial airways and mechanical ventilation (MV), length of ICU stay and ICU survival were recorded. The occurrence and frequency of yawning were recorded by ICU nursing staff [20]. All patients were followed until death or discharge from the ICU.

Statistical analysis was performed using a computer program (SPSS for Windows, version 10.0, Chicago, IL, USA). Values were expressed as mean ± standard deviation (SD), unless otherwise specified. Pearson's product-moment correlation was used to assess the relationship between 2 continuous variables. To investigate the prognostic factors, proportions of variables were compared with the chi-square test. Variables with $p<0.20$ in the univariate analysis were selected to enter the multivariate analysis. A multivariate logistic regression was used to determine the independent relationship between yawning and clinical outcomes. A life table was computed using the Kaplan-Meier method. A 2-tailed p value of <0.05 was considered significant.

Results

Comparisons between critically ill patients who had yawned and those who had not yawned in the ICU are shown in Table 1. Factors associated with yawning in the ICU are shown in Table 2 (variables with a $p<0.20$ in Table 1 were selected and entered in a logistic regres-

Table 1. Comparisons between critically ill patients who had yawned and those who had not yawned in the ICU

Variables	All	Had not yawned	Had Yawned	*p* value
No (%)	99	51	48	
Age, yr	64.6 ± 18.2	63.3 ± 18.6	66.0 ± 17.9	0.467
Male, n (%)	61 (61.6)	32 (62.7)	29 (60.4)	0.839
Incidence of yawning per day, %*	22.1 ± 6.9	0	39.9 ± 10.4	
Frequency of yawning per day+	0.5 ± 1.3	0	0.9 ± 1.6	
Main diagnosis category, n (%)‡				
Sepsis	57 (57.6)	32 (62.7)	25 (52.1)	0.314
Shock	21 (21.2)	15 (29.4)	6 (12.5)	0.050
Neurological	33 (33.3)	12 (23.5)	21 (43.8)	0.054
Cardiovascular	24 (24.2)	13 (25.5)	11 (22.9)	0.818
Respiratory	37 (37.4)	17 (33.3)	20 (41.7)	0.414
Gastrointestinal bleeding	24 (24.2)	14 (27.5)	10 (20.8)	0.489
Cirrhosis	19 (19.2)	13 (25.5)	6 (12.5)	0.128
Uremia	11 (11.1)	6 (11.8)	5 (10.4)	1.000
Diabetes Mellitus	29 (29.3)	13 (25.5)	16 (33.3)	0.508
Cancer	18 (18.2)	12 (23.5)	6 (12.5)	0.196
Cardiac arrest	6 (6.1)	4 (7.8)	2 (4.2)	0.679
Medications, n (%)‡				
Sedatives	53 (53.5)	24 (47.1)	29 (60.4)	0.228
Vasopressors	33 (33.3)	22 (43.1)	11 (22.9)	0.036
Steroids	31 (31.3)	16 (31.4)	15 (31.3)	1.000
Muscle relaxants	2 (2.0)	1 (2.0)	1 (2.1)	1.000
APACHE II score	20.1 ± 9.7	22.0 ± 10.9	18.0 ± 7.8	0.038
TISS	26.9 ± 10.7	29.1 ± 11.7	24.6 ± 9.0	0.037
SIRS score on day 1	2.4 ± 1.3	2.6 ± 1.2	2.1 ± 1.2	0.041
SOFA score on day 1	6.7 ± 4.2	7.3 ± 4.2	6.1 ± 4.0	0.150
Oxygen requirement, n (%)	87 (87.9)	48 (94.1)	39 (81.3)	0.066
Artificial airways, n (%)	55 (55.6)	28 (54.9)	27 (56.2)	0.905
Endotracheal tube	50 (50.5)	25 (49.0)	25 (52.1)	
Tracheostomy	5 (5.1)	3 (5.9)	2 (4.2)	
Mechanical ventilation (MV), n (%)	58 (58.6)	31 (60.8)	27 (56.3)	0.687
Non-invasive	3 (3.0)	3 (5.9)	0 (0)	
Invasive	55 (55.6)	28 (54.9)	27 (56.3)	
Length of MV, days	5.9 ± 8.6	3.1 ± 4.1	8.8 ± 11.0	0.001
Length of ICU stay, days	8.1 ± 7.8	5.1 ± 3.4	11.3 ± 9.7	<0.001
ICU Mortality, n (%)	22 (22.2)	17 (33.3)	5 (10.4)	0.008

* Percentages of persons who yawned each day were averaged over 1 week.

+ Average daily yawning frequency over 1 week (total = 486 patient-days in all patient groups and 263 patient-days in the had-yawned group).

‡ Number of diagnoses or medications for each patient may be more than one. TISS: simplified Therapeutic Intervention Scoring System; SIRS: systemic inflammatory response syndrome; SOFA: Sequential Organ Failure Assessment.

Table 2. Factors associated with yawning in the ICU (Variables with a $p<0.20$ in Table 1 were selected and entered in a logistic regression model)

Variables	Adjusted OR	95% CI	*p* value
Diagnoses			
Neurological	3.06	1.78-7.96	0.022
Shock	0.32	0.10-0.99	0.047
APACHE II score ≥ 20	0.32	0.13-0.75	0.009

OR: odds ratio; CI: confidence interval.

sion model).

Of 99 patients, 48 were observed to have yawned at least once in the ICU. The incidence of observed yawning in the ICU was 9.1%-32.5% each day (Figure 1). About 47% (27/58) of those receiving invasive MV had yawned (Table 1). Patients who had not yawned tended to have non-neurological diagnoses (p=0.035) or shock (p=0.045), or used vasopressors (p=0.035), and were more seriously ill as measured by the APACHE II score (p=0.004), compared to those who had yawned (Table 2).

In the logistic regression model, we found that only the presence of yawning (adjusted odds ratio [OR] 0.24, 95% CI 0.06-0.94, p=0.04) and use of vasopressors (adjusted OR 9.9, 95% CI 2.55-38.45, p=0.001) were independently associated with ICU mortality among MV patients (Table 3 and Figure 2).

Discussion

This is the first study to investigate the characteristics of yawning in the medical ICU, and whether yawning, as a measure of brain function, could have implications in patient outcome. We found that yawning was a relatively uncommon observation in daily ICU care, with a lower incidence and frequency compared with healthy persons. Whether the patients were receiving invasive MV or not, yawning occurred in about 50% of the critically ill patients during their stay in the ICU, and was more commonly observed in certain patients who were less severe and had neurological diagnoses. MV patients who had yawned in the ICU were more likely to survive their critical illnesses.

Since inhalation to near total lung capacity during a yawn might prevent atelectasis [2, 21],

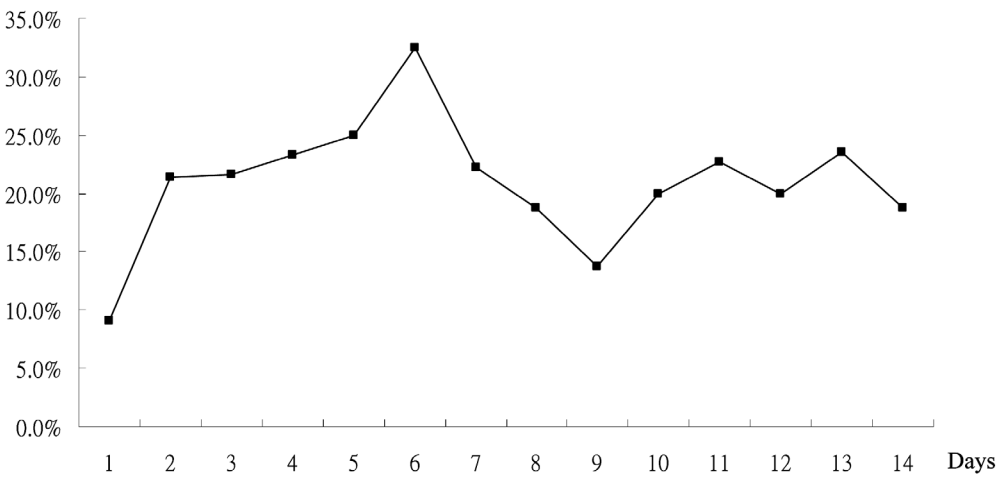

Fig. 1. Daily observed yawning percentage (number of patients who had yawned divided by the number of patients) in the ICU.

Table 3. Factors associated with ICU mortality (Variables with a $p<0.20$ were selected and entered in a logistic regression model)

	Univariate analysis		Multivariate analysis*	
Variables	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Yawning	0.23 (0.08-0.69)	0.009	0.24 (0.06-0.94)	0.040
Diagnoses				
Shock	3.75 (1.31-10.71)	0.014		NS
Cancer	2.80 (0.93- 8.42)	0.067		NS
CPR	8.33 (1.41-49.10)	0.019		NS
SIRS score on day 1				
0-1	1.00			
2-5	4.53 (0.98-20.94)	0.053		NS
APACHE II score				
< 20	1.00			
≥ 20	10.48 (2.85-38.54)	<0.001		NS
TISS				
< 26	1.00			
≥ 26	11.73 (3.18-43.23)	<0.001		NS
SOFA score				
< 6	1.00			
≥ 6	4.62 (1.43-14.91)	0.010		NS
Use of vasopressors	18.6 (5.48-63.09)	<0.001	9.9 (2.55-38.45)	0.001
Mechanical ventilation	1.61 (1.31-1.97)	<0.001		NS
Oxygen		0.063		NS

* Since there were no deaths among the patients without MV, only those with MV were included in the multivariate analysis; OR: odds ratio; CI: confidence interval; CPR: cardiopulmonary resuscitation; NS: not significant.

yawning has been proposed as a therapeutic maneuver to prevent pulmonary complications in postoperative patients [22]. However, yawning does not serve a primary respiratory function and is not triggered by the changes in environmental carbon dioxide or oxygen levels [23]. In our study, although patients without oxygen therapy tended to yawn more, the difference was not significant (Table 1). Besides, we found that the occurrence of yawning was similar between those with/without the use of artificial airways or MV, which supports the concept of different control mechanisms for yawning and breathing. Healthy persons yawned about 8.7 times per day in a previous field observation [24], which showed that yawning is associated with changes in an individual's activity or arousal level.

Yawning can be classified as physiological or pathological [1-4, 25]. Physiological yawning can be triggered internally by changes in body states (fatigue, boredom, sleep or arousal) [1], or externally by hearing, seeing or thinking about someone else yawning (i.e., contagious yawn) [3-4]. Pathological (or excessive) yawning can occur in various neurological diseases such as migraine, Parkinson's disease, hypophyseal tumor, temporal lobe epilepsy and acute brain stem ischemia [1-2, 25], suggesting that both the lower brain stem and cortical-subcor-

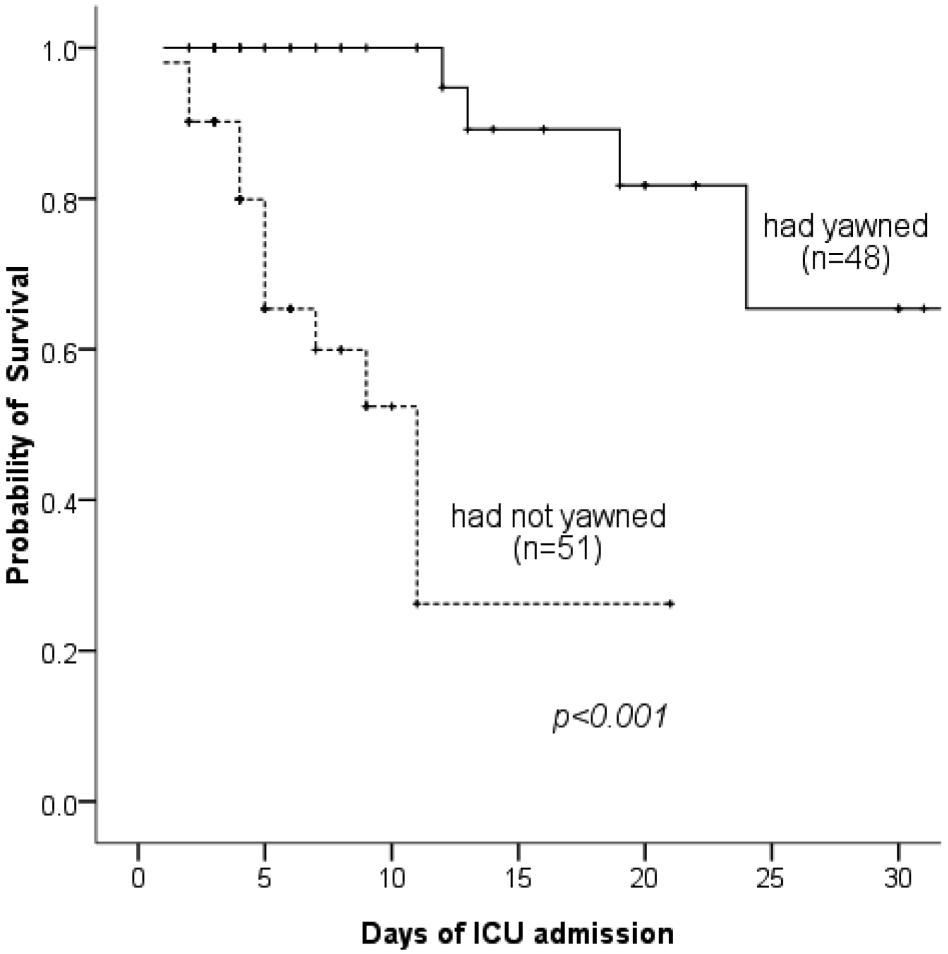

Fig. 2. Yawning versus ICU mortality. This Kaplan-Meier plot shows the relationship between yawning and mortality in the ICU, using the classification of "had yawned" and "had not yawned" in the ICU.

tical brain areas are involved in the control of yawning [25-26]. In addition, the yawning-triggering structures in the PVN of the hypothalamus may be linked to 3 distinct efferent outputs, projecting to respiratory, cardiovascular and arousal systems [27]. This complex neuro-anatomical yawning reflex is modulated by nitric oxide, hormones (oxytocin, ACTH, corticosteroids, androgen) and neurotransmitters (dopamine, acetylcholine, serotonin, gamma-aminobutyric acid [GABA]) [1, 25]. Accordingly, several clinical and laboratory applications of yawning have been suggested [1-4, 25-31]: it has been used as an expression of therapeutic dopaminergic activity in Parkinsonism and migraine [1, 13, 28], a biological marker of heroin-dependence disorders [29], a monitoring for depth of anesthesia with GABA agonists [30], a clinical sign in intracranial hypertension, migraine, or iatrogenic side effects of dopaminergic drugs and serotonin reuptake inhibitors [1, 12-13, 31], and for preclinical drug evaluation [13].

Until recently, yawning in critically ill patients was rarely studied. In a study of traumatic brain-injured (TBI) comatose patients who were

still mechanically ventilated and without clinical signs of awareness after 2 weeks (despite a sedation cessation >48 h), yawning was observed in 19% and was more commonly observed in those with a permanent vegetative state or major sequelae (29% vs. 6%, $p<0.01$) [20]. However, the occurrence of yawning during the acute stage of TBI was not independently associated with the neurological outcome assessed at 1 year [20]. In our study, yawning was also not commonly observed in the medical ICU, especially in patients with more severe illnesses or non-neurological diagnoses. Because of the different patient populations, however, it is difficult to compare the 2 studies.

There are several reasons to expect some changes in yawning during critical illnesses. First, REM sleep deprivation in rats can impair yawning and stretching behavior [6]. A surge in plasma ACTH levels at night and just prior to awakening from sleep is associated in humans with yawning and stretching behavior [5]. Second, stressful manipulations have been reported to modify drug-induced yawning, which is diminished by constant, and increased by intermittent stress [7]. Third, yawning in rats is suppressed by adrenectomy and reverted by dexamethasone administration, suggesting the implication of stress hormones in the modulation of this behavior [8-9]. Finally, yawning can be either induced (by morphine, dextromethophan, propofol) or suppressed (by metoclopramide and haloperidol), according to the central pharmacological activity of the commonly used medications in the ICU [1, 31]. Since critical illnesses represent a stressful condition, in which sleep disruption, altered mental status and relative adrenal insufficiency frequently occur and are related to disease severity [14-15], the finding of decreased yawning in this study was not unexpected. Besides, we also found that several factors, including severity of acute illnesses, shock or use of vasopressors, and neurological diseases, were associated with the occurrence of yawning. Although the absence of yawning in MV patients was associated with increased mortality, this does not imply that yawning is vital to survive. Instead, it may be only an epiphenomenon, since several other important factors, such as the occurrence of delirium or encephalopathy, sleep deprivation and use of medications (especially sedatives/analgesics), might also have implication in the occurrence of yawning and patient outcome [14-15]. Further studies are required.

We are aware that several limitations were present in this study. First, medications which have effects on yawning were not investigated. Second, the method of recording yawning may be inaccurate; therefore, the occurrence of yawning in these patients might be underestimated. However, compared with less severe patients, those with more severity would receive more nursing care and monitoring; therefore, theoretically, observed yawning would be more common in the latter group if there was no difference between the 2 groups. Instead, more yawns were recorded in the less severe group, which implies that the difference in yawning incidence between them should be a real phenomenon. Third, although we found that patients with neurological diagnoses yawned more, the occurrence of delirium or encephalopathy and the contribution of different neurological diseases were not studied.

In conclusion, the characteristics of yawning in critically ill patients were quite different from those of healthy persons. The finding of an association between the absence of yawning and increased mortality in the MV patients is

very interesting, and may be used as a prognostic sign, but further studies using a more accurate method, such as video recording, are required.

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打哈欠出現在使用呼吸器的重症患者時可視爲一個存活指標

沈修年　杜漢祥　丁郁茹*　陳美偵*　沈美麗*　呂瑾立**　鄭高珍

背景：打哈欠的行為可用來當作中樞dopaminergic system的功能性指標，而其神經控制路徑也屬於與同理心有關的神經網絡活動的一部分。打哈欠的產生也就是此神經功能區運作的表現。因為重症患者常有腦病變的併發症，其發生也會影響預後。此研究即假設以打哈欠做為一種中樞神經功能的表現，來探討打哈欠的出現與否和重症患者的預後是否有關。

方法：從2006年7月到11月，我們前瞻性地研究了99位陸續住到在南部某醫學中心內科加護病房的患者。其打哈欠的發生與頻率由加護病房的照護護士記錄之。然後再以多變數邏輯分析來測定打哈欠與臨床預後的獨立相關性。

結果：不管是否有使用機械通氣，約有一半的患者在加護病房中至少有一次被觀察到有打哈欠的行為。和曾出現打哈欠者比較，未曾出現打哈欠的患者較常有非神經性疾病診斷（p=0.035）、休克（p=0.045）或使用血壓升壓劑（p=0.035），而且疾病嚴重度較高（p=0.004）。在多變數邏輯分析模型中，我們發現在使用機械通氣的重症患者中，與加護病房死亡率有獨立相關的因素只有兩個：曾出現打哈欠（adjusted odds ratio [OR] 0.24, 95% CI 0.06-0.94, p=0.04）與使用血壓升壓劑（adjusted OR 9.9, 95% CI 2.55-38.45, p=0.001）。

結論：在內科加護病房的重症患者並不常出現打哈欠。然而，若觀察到使用呼吸器的重症患者有打哈欠的行為，將可以期待其預後會較為樂觀。*(胸腔醫學* ***2009; 24: 1-10)***

關鍵詞：打哈欠，機械通氣，重症，預後

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The Clinical Outcome of Surgically-Proved Cryptogenic Organizing Pneumonitis

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Background: Cryptogenic organizing pneumonitis (COP) is a specific clinicopathological syndrome characterized by chronic inflammation and a proliferation of granulation tissue within the small airways and alveolar ducts. This report summarized the clinical features of 23 patients with surgically-proved COP and discussed the therapy as well as the outcome of different clinicoradiological patterns of COP.

Methods: Twenty-three patients who had surgically-proved COP, from January 1994 to June 2006 at Kaohsiung Veterans General Hospital, were retrospectively evaluated using their radiological images, pulmonary function tests, treatment and prognosis. These patients were classified into 3 groups: (1) COP with a focal pulmonary pattern, (2) COP with a pulmonary consolidation pattern and (3) COP associated with connective tissue diseases.

Results: All patients with COP with a focal pulmonary pattern, who received surgical resection alone, had an excellent outcome without local recurrence. Of 11 patients with COP with a pulmonary consolidation pattern who received 2 to 12 months of corticosteroid therapy, 8 (73%) showed marked improvement in both clinical symptoms and pulmonary function test results. Of the 4 patients with COP associated with connective tissue diseases, 3 who received combined corticosteroid and cytotoxic drug therapy had improvement. The remaining patient, who had initial steroid therapy alone, showed no significant improvement, but had a better response after receiving combined treatment with corticosteroid and cytotoxic drugs.

Conclusions: COP must be considered in the differential diagnosis of focal nodular lesions. Patients with COP with a pulmonary consolidation pattern characterized by flu-like illness, bilateral crackles and patchy infiltrates had an overall favorable prognosis with corticosteroid therapy. In patients with COP associated with connective tissue diseases, steroid therapy alone may be inadequate. In our limited series of cases, steroid in combination with cytotoxic therapy was effective. ***(Thorac Med 2009; 24: 11-19)***

Key words: cryptogenic organizing pneumonia (COP), idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), corticosteroid, connective tissue diseases

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Introduction

Cryptogenic organizing pneumonitis (COP), also called idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), is a pathological pattern common to a variety of clinical pulmonary disorders. The major histological changes that comprise COP are organizing pneumonia with intraluminal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli), a patchy distribution, preservation of lung architecture, uniform temporal appearance and mild interstitial chronic inflammation [1-3]. COP may be secondary to lung injury especially resulting from infection and drug toxicity [4-5], or may be developed in the context of connective tissue diseases [1, 6]. COP may also be idiopathic and present as the hallmark of a distinct clinicoradiological syndrome of subacute pneumonia, with typical alveolar patchy opacities on imaging. In COP with a pulmonary consolidation pattern, corticosteroid therapy was highly effective and the response rate was reported to be 65% to 97% [1-2, 7-12]. In contrast, patients with COP associated with connective tissue diseases had a poorer outcome [13-14]. It is important for clinicians to determine the differences between the clinical variants of COP, especially when considering diagnosis, treatment and prognosis. We examined the clinical features and outcomes of 3 clinical variants of COP: COP with a focal pulmonary pattern, COP with a pulmonary consolidation pattern and COP associated with connective tissue diseases.

Methods and Materials

From January 1994 to June 2006, 26 patients were surgically proved to have COP at Kaohsiung Veterans General Hospital. We excluded 3 patients using the following clinical exclusion criteria in the initial medical history review: COP associated with proved infectious pneumonia, pulmonary tuberculosis, lung abscess or empyema (n=2), and COP diagnosed at resection for lung cancer (n=1). Patients with a focal pulmonary nodule or mass showing only COP pathology on biopsy with no new pulmonary symptoms and no underlying causes were defined as COP with a focal pulmonary pattern. Symptomatic patients with areas of consolidation or patchy infiltrates on chest radiography, COP pathology and no recognized underlying causes were classified as COP with a pulmonary consolidation pattern (Figure 2). Patients with dyspnea combined with immunological manifestations such as skin erythematous change and arthralgia, as well as radiological findings, such as consolidations and infiltrations with COP pathology, were regarded as COP associated with connective tissue diseases.

Histopathologic specimens from lung surgical biopsies of the 23 patients were reviewed by a pathologist to confirm the presence of

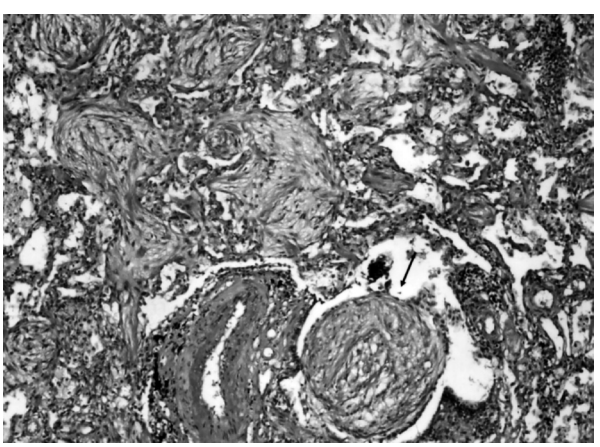

Fig. 1. Histology section shows polypoid plugs of loosely organizing connective tissue protruding into the lumen of a bronchiole (arrow) and the alveolar spaces. (H & E 100X)

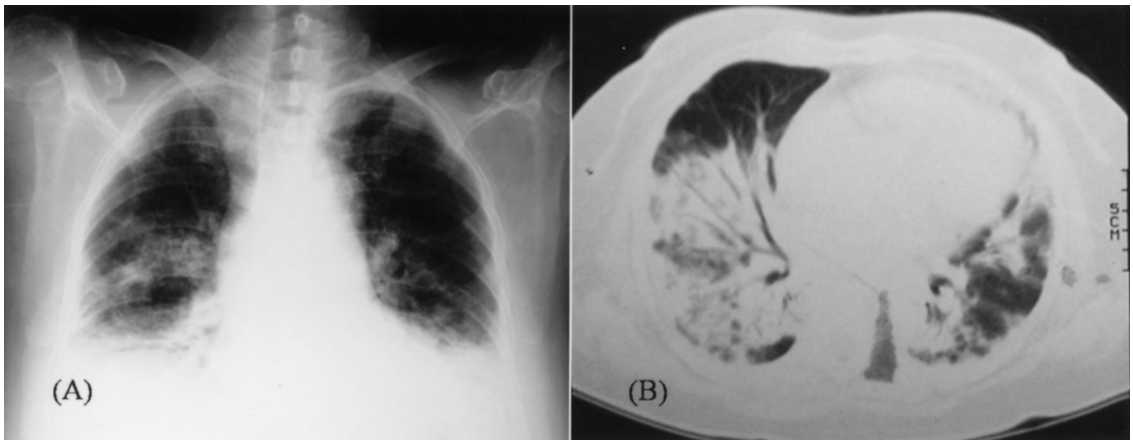

Fig. 2. Cryptogenic organizing pneumonitis with multiple patchy opacities. (A) Chest X-ray showing bilateral patchy infiltrates. (B) CT scan showing consolidation with air bronchogram.

typical COP (Figure 1). Data were obtained by comprehensive review of medical records and radiographic findings. Symptoms assessment included cough, dyspnea, sputum production, hemoptysis, fever >38°C and the presence of flu-like syndromes. Clinical signs included tachypnea, crackles, wheezing, clubbing and cyanosis. Pulmonary function test data included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and ratio of FEV1 to FVC. All chest radiographs and chest computed tomography (CT) scans from the time of initial presentation were reviewed by a radiologist to assess the type and distribution of lung patterns.

The initial features for the 3 groups of COP were analyzed using proportion and percentage for categorical variables and mean (± SD) for continuous variables. All the patients were followed up at the outpatient clinic for more than 18 months. We recorded the results using the time for resolution in the chest radiography, drug dosage, duration of medical treatment and outcome as factors.

Results

Eight patients had COP characterized as COP with a focal pulmonary pattern, 11 had COP with a pulmonary consolidation pattern, and 4 had COP associated with connective tissue diseases. The third group of patients included 3 with systemic lupus erythematous (SLE) and 1 with dermatomyositis.

Patient Characteristics

The mean age of the patients with COP with a pulmonary consolidation pattern was greater than that of the other 2 groups (Table 1). Patients with COP with a pulmonary consolidation pattern and COP associated with connective tissue diseases had similar initial symptoms, the most common of which were a new onset of cough and dyspnea (Table 1). The group with COP with a focal pulmonary pattern had no new constitutional or pulmonary symptoms. The symptomatic patients in this group were smokers with longstanding symptoms. The mean duration of symptoms from onset to diagnosis was 4 weeks for patients with COP with a pulmonary

Table 1. Patient Characteristics at Time of Diagnosis and Initial Symptoms and Signs

Variables	COP proportion (%)		
	Focal (n=8)	Idiopathic (n=11)	Secondary (n=4)
Mean (± SD) age, y	57.0 (9.2)	66.4 (11.0)	52.3 (7.8)
Gender M/F	3/1	6/5	5/3
Symptoms			
Cough	7/8 (87.5)	11/11 (100)	1/4 (25.0)
Dyspnea	1/8 (12.5)	10/11 (90.9)	4/4 (100)
Phlegm	5/8 (62.5)	7/11 (63.6)	0/4 (0)
Hemoptysis	2/8 (25.0)	0/11 (0)	0/4 (0)
Fever	3/8 (37.5)	3/11 (27.3)	2/4 (50)
Signs			
Tachypnea	1/8 (12.5)	10/11 (90.9)	4/4 (100)
Crackles	0/8 (0)	10/11 (90.9)	4/4 (100)
Wheezing	0/8 (0)	3/11 (27.3)	0/4 (0)
Clubbing	0/8 (0)	0/11 (0)	0/4 (0)
Cyanosis	0/8 (0)	0/11 (0)	0/4 (0)

consolidation pattern and 6 weeks for patients with COP associated with connective tissue diseases. The most frequent physical findings were crackles and tachypnea. Signs of airflow obstruction were rarely described. Due to the lack of symptoms, most patients in the COP with a focal pulmonary pattern group were discovered by incidental radiological findings.

The radiographic findings of the 3 variants of COP were classified into 3 categories (Table 2): bilateral multifocal consolidations, diffuse bilateral lung infiltrations, and unifocal region of consolidation or nodule. Eleven of the 23 patients in our study had idiopathic COP in which the most common radiological manifestation was diffuse infiltrative lung diseases (63.6%).

Restrictive respiratory impairment, manifested by a decrease in forced vital capacity, diffusing capacity, and arterial O_2 tension (PaO_2), was more commonly seen in the idiopathic COP and secondary groups than in the COP with focal pulmonary pattern group. Most patients in the focal group had a normal flow-volume curve.

Clinical Course, Treatment Duration and Outcome

Six of the 8 patients with COP with a focal pulmonary pattern underwent lobectomy and the other 2 received wedge resection. None of these patients were given corticosteroids and there was no relapse or subsequent signs or symptoms.

Eight of the 11 patients with COP with a pulmonary consolidation pattern who received 2 to 12 months of glucocorticosteroid therapy showed great improvement in both clinical symptoms and pulmonary functions. One patient felt improvement subjectively, but the pulmonary function test (PFT) showed no significant changes. One patient suffered from persistent symptoms and showed gradual worsening

Table 2. Chest Radiographic Findings

Primary Radiologic Abnormality	Primary Diagnosis of COP, proportion (%)		
	Focal (n=8)	Idiopathic (n=11)	Secondary (n=4)
Multifocal areas of consolidation	0/8 (0)	4/11 (36.4)	0/4 (0)
Diffuse infiltrative lung diseases	0/8 (0)	7/11 (63.6)	4/4 (100)
Focal nodule or mass	8/8 (100)	0/11 (0)	0/4 (0)

in both imaging findings and FVC. The mean time for resolution on chest radiography was 4.1 ± 2.6 months. The mean duration of steroid treatment was 7.6 ± 5.5 months. Two patients received prednisolone for more than 12 months (14 and 18 months) due to lack of a clinical response. Among the 8 patients receiving steroid treatment, 4 had only short-course treatment for less than 4 months.

In the secondary COP group, 3 of the 4 patients had extra-pulmonary symptoms such as skin and facial rash, and arthralgia, in addition to dyspnea, and were diagnosed with SLE by the rheumatologist at the same time. These patients received steroid and cytotoxic drug treatment (parenteral methylprednisolone and cyclophosphamide, followed by oral prednisolone and azathioprine). The remaining patient had only respiratory symptoms as an initial presentation. He received steroid therapy initially, but with a poor response. Erythematous papules and plaques ensued 4 months later. The dermatologist performed skin biopsy, which confirmed the diagnosis of dermatomyositis. His respiratory symptoms improved and the patchy infiltrations resolved after cytotoxic drug prescription. However, the disease recurred 8 months later. He received high-dose steroid and cytotoxic drug therapy once again, but died from septic shock. The mean time for resolution on chest radiography was 5.8 ± 5.0 months. Low-dose prednisolone with or without cytotoxic drugs were prescribed for this patient for more than 1 year, not only for treating COP, but also for the underlying collagen vascular disease.

Discussion

The definition of the typical presentation of COP with a pulmonary consolidation pattern is drawn from a large number of histologically and clinically-based series published in the last 15 years [1, 7, 9, 11-16] and is summarized in several review articles and commentaries [13, 18-20]. After the diagnosis of COP has been made histologically or empirically, corticosteroid therapy is generally instituted. In most patients, the response is excellent, with reported rates of 65% to 97% [1-2, 7-10, 15]. In our series, 8 of the 11 patients (73%) with COP with a pulmonary consolidation pattern who received 2 to 12 months of glucocorticosteroid therapy showed great improvement in both clinical symptoms and pulmonary functions. The better outcome in COP patients with a pulmonary consolidation pattern, as compared with those with secondary organizing pneumonia, tended to obscure a small but important subgroup of patients with COP with a pulmonary consolidation pattern, as presented in most large series, whose disease was resistant to treatment. The striking variability in presentation and outcome

in COP with a pulmonary consolidation pattern was first documented in a report of 16 patients with COP with a pulmonary consolidation pattern, 12 of whom did not follow the "classical" course [16]. Circumstantial support for this observation has been provided in a number of subsequent series. The prediction of outcome in COP with a pulmonary consolidation pattern can be subdivided into the early detection of factors associated with a poor long-term outcome and the identification of those at higher risk of short-term relapse after a good response. Neither question has been widely studied, in part because few series had sufficient patients to allow sophisticated statistical evaluation, but also because of the recent identification of a significant subgroup of patients with COP with a pulmonary consolidation pattern who will develop progressive pulmonary fibrosis. Among our patients, there were no major differences in symptoms and chest radiographic findings between steroid-sensitive patients and non-responders.

Although it is universally accepted that oral corticosteroid therapy is the treatment of choice, there are no universally agreed guidelines regarding the dose and duration of treatment. Initial prolonged high-dose therapy consisting of 1mg/kg/day of prednisolone for 1 to 3 months, decreasing to 40 mg daily for 3 months, and then to 10 mg daily (or 20 mg on alternate days) for 1 year, has been advocated [14]. However, another report argued compellingly that relapse could be easily controlled and would not adversely affect the long-term outcome, thus a lower initial corticosteroid dosage and a shorter duration of treatment (4 to 6 months) were warranted [22]. Many clinicians adopt an intermediate approach, which is usually tailored to the level and duration of treatment to minimize adverse side effects. In our patients with a good clinical response, the dosage and duration varied widely. There was no relapse, in contrast to reported rates of relapse of 9% [2, 11] to 58% [23] in case series with more than 15 patients.

An important subgroup that presents with focal lung lesions, often manifesting as a solitary pulmonary nodule on chest radiography, is associated with an excellent outcome [15-16, 23]. The systemic features of COP with a pulmonary consolidation pattern are usually lacking and lung malignancy is often suspected, which leads to empirical surgical resection. As a rule, treatment is not required, the disease will not relapse, and there are no respiratory deaths during follow-up [10]. The prevalence of this subgroup is difficult to estimate. It is seldom possible to exclude lung malignancy in focal organizing pneumonia initially, based upon chest radiographic and CT features, and surgical resection is usually required.

An early distinction in outcome was made between COP with a pulmonary consolidation pattern and organizing pneumonia associated with connective tissue diseases. One study found that a small group of patients with connective tissue diseases tended to have a poor outcome, in contrast to the remaining cases [1]. It subsequently became apparent that a significant proportion of those with connective tissue diseases did well with treatment. Of the first 37 patients reported, 25 responded satisfactorily to corticosteroid therapy with or without immunosuppressive agents [21]. However, disease progression was observed in one-third of cases, a proportion much higher than in series of patients with COP with a pulmonary consolidation pattern. Recent reports have consistently confirmed the poorer outcome for organizing

pneumonia associated with other diseases, with a 5-year survival rate of 44% in 27 patients in 1 series [10] and similar results in much smaller subgroups in other reports. In our series, the 3 patients improved soon after corticosteroid and cytotoxic drug combination therapy. The respiratory symptoms and diagnosis of COP in the remaining patient preceded the discovery of associated collagen vascular disease. He received steroid therapy initially, but had a poor response. After dermatomyositis was diagnosed and a cytotoxic drug was added, his symptoms improved. Therefore, if a patient has COP with a pulmonary consolidation pattern that is refractory to corticosteroid treatment, a thorough physical examination and autoimmune profiles evaluation is recommended. Based on our experience with this limited number of cases, corticosteroid and cytotoxic drugs may be adequate for this group of patients.

Conclusions

COP with a pulmonary consolidation pattern characterized by flu-like illness, bilateral crackles and patchy infiltrates had an overall favorable prognosis with corticosteroid therapy. COP must also be considered in the differential diagnosis of focal nodular lesions. In this study, patients with COP with pulmonary consolidation had a good response (73%) to steroid therapy. In patients with COP associated with connective tissue diseases, steroid therapy alone may be inadequate. Our experience with this limited number of cases revealed that steroid in combination with cyclophosphamide therapy may be effective.

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手術證實之原因不明器質化肺炎之臨床結果

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背景：原因不明器質化肺炎是一種非特異性的病理形態，常見於肺部的發炎性疾病。其病理組織的特徵為鬆散的節締組織積聚在細小支氣管及肺泡。

方法：自1994年1月到2006年6月共有23位病人經由外科手術切片診斷為原因不明器質化肺炎。這些病人可分為三組：局部肺病灶型、原因不明的有機化肺炎（或稱作原發性阻塞性細支氣管炎併有機化肺炎）、以及自體免疫疾病相關的原因不明器質化肺炎。

結果：局部肺病灶型病人在外科手術切除後不再復發，亦不需類固醇治療。原因不明器質化肺炎是一種臨床病理症候群，11位病人中有8位（73%）在為期2至12個月類固醇治療後反應良好。自體免疫疾病相關的原因不明器質化肺炎對類固醇治療反應較差。在我們有限的病例中加上細胞毒性藥物可以改善症狀。

結論：在局部肺病灶的鑑別診斷過程中原因不明器質化肺炎是要考慮的。原因不明器質化肺炎併有雙側聽診之濕囉音及斑塊狀浸潤使用類固醇治療有良好之預後。與結締組織疾病相關之原因不明器質化肺炎，只有類固醇治療可能是不適當的。在我們有限的病患裡，類固醇併用細胞毒性藥物治療其預後更好。*(胸腔醫學* ***2009; 24: 11-19)***

關鍵詞：原因不明器質化肺炎，阻塞性細支氣管炎併有機化肺炎，類固醇，結締組織疾病

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Intravenous Immunoglobulin Therapy in a Patient with Tuberculosis-associated Hemophagocytic Syndrome: A Case Report

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Hemophagocytic syndrome is an uncommon but severe fatal condition associated with a variety of infectious agents, as well as genetic, neoplastic, and autoimmune diseases. We report a 63-year-old man presenting with severe shock, acute respiratory distress syndrome, and multi-organ failure. Hemophagocytic syndrome was suspected due to the high level of serum ferritin and cytopenia, and was confirmed by bone marrow aspiration. His hemodynamic status, cytopenia, and oxygenation improved dramatically after administration of intravenous immunoglobulin for 2 consecutive days. Tuberculosis was confirmed by positive polymerase chain reaction for tuberculosis in the sputum and blood, and later by sputum mycobacterium culture. He recovered uneventfully and was successfully weaned from the ventilator. This case highlights disseminated tuberculosis as a potential cause of HPS; immediate intravenous immunoglobulin administration may rescue the patient from the catastrophic state. ***(Thorac Med 2009; 24: 20-26)***

Key words: hemophagocytic syndrome, intravenous immunoglobulin, tuberculosis

Introduction

Hemophagocytic syndrome (HPS) is a disorder characterized by fever, lymphadenopathy, hepatosplenomegaly, cytopenia, and hyperferritinemia due to dysregulated activation and proliferation of macrophages, leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes, and their hematopoietic precursors throughout the reticuloendothelial system [1].

HPS is classified as familial and reactive, and may be associated with infections - including bacterial, viral, fungal and parasitic infections - malignancy, autoimmune diseases, or drugs. Tuberculosis is one of the uncommon infections that cause HPS, but is associated with high mortality. We describe a case of HPS secondary to disseminated tuberculosis, complicated with septic shock and multi-organ failure, and treated successfully with intravenous immunoglobulin.

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Case Report

A 63-year-old male presented with unproductive cough for 2 weeks, followed by fever, general malaise, weakness, myalgia, sore throat and fever. He sought medical help at a local clinic, where vomiting, diarrhea, and yellowish coloration of the skin were noted. He was admitted to the local hospital due to progressive shortness of breath and low urine output. Empiric antibiotics and steroid were given. Endotracheal intubation and mechanical ventilation were begun under the impression of acute respiratory failure, and hemodialysis was performed for acute renal failure with metabolic acidosis. Transfusion with packed red blood cells and platelets was also performed. Laboratory data revealed the following: total leukocyte count: 2,600 /μl; hemoglobin: 13.2 g/dl and platelet count: 24,000 /μl; C-reactive protein (CRP): 18.3 mg/dl; blood urea nitrogen (BUN): 100 mg/dl; creatinine: 8.4 mg/dl; aspartate aminotransferase (AST): 256 U/l; alanine aminotransferase (ALT): 151 U/l; total bilirubin: 6.1 mg/dl; prothrombin time (PT): 19.6 sec (control 11.8 sec); international normalized ratio (INR): 1.72; and activated partial thromboplastin time (aPTT): 61.6 sec (control: 28.8 sec). Due to persistent hypoxemia and an unstable hemodynamic status, the patient was transferred to our Emergency Department.

The patient had had pneumoconiosis for nearly 20 years, and had an occupational history as a coal miner. He did not use any medications and had not traveled abroad. He had smoked 1 to 2 packs of cigarettes per day for 40 years, and drank alcohol on social occasions only. There was no family history of tuberculosis.

On physical examination, the patient was acutely ill-looking, and his skin appeared dehydrated. His body temperature was 35.2^{o}C, blood pressure: 68/27 mmHg, heart rate: 109 beats per minute, and respiratory rate: 40 per minute. Head and neck examination revealed pale conjunctiva and icteric sclera, but no lymphadenopathy. Chest examination revealed symmetrical expansion with diffuse crackles bilaterally. Heart sounds revealed a regular rhythm with no murmur. Bowel sounds were hypoactive and bilateral lower legs showed minimal pitting edema.

Laboratory data revealed a total leukocyte count of 14,000/μl with a left shift (94.5% neutrophils, 4.8% lymphocytes, 0.3% monocytes, 0.3% eosinophil, 0.1% basophils); hemoglobin: 10.2 g/dl; and platelet count: 131,000 /μl. Biochemistry studies revealed BUN: 62 mg/dl; creatinine: 5.7 mg/dl; AST: 341 U/l; total bilirubin: 7.6 mg/dl; PT: 12.1 sec (control: 11.6 sec, INR: 1.1); aPTT: 68.0 sec (control: 27.5 sec); lactate dehydrogenase (LDH): 660 U/L; D-dimer 5,562 ng/ml. The chest radiograph on admission revealed bilateral alveolar infiltration with diffuse micronodules in both lung fields (figure 1A). Arterial blood gas with 100% oxygen revealed pH: 7.114; PCO_2: 51.1 mmHg; PO_2: 43.0 mmHg; HCO_3-standard: 13.7 mmol/l; oxygen saturation: 63.7%.

After admission, mechanical ventilation was continued, along with hemodialysis with continuous venovenous hemodialysis (CVVHD). Empiric antibiotics with Rocephine (ceftriaxone), Cravit (levofloxacin), penicillin-G and Tamiflu (oseltamivir phosphate), vasopresser agents with dopamine and Levophed (norepinephrine), and steroid were administered. A Swan-Ganz catheter was inserted and showed cardiac output of 7.83 L/min, pulmonary wedge systolic pressure (PWSP) of 15 mmHg, and a cardiac index of 4.72 L/min. Cardiac echog-

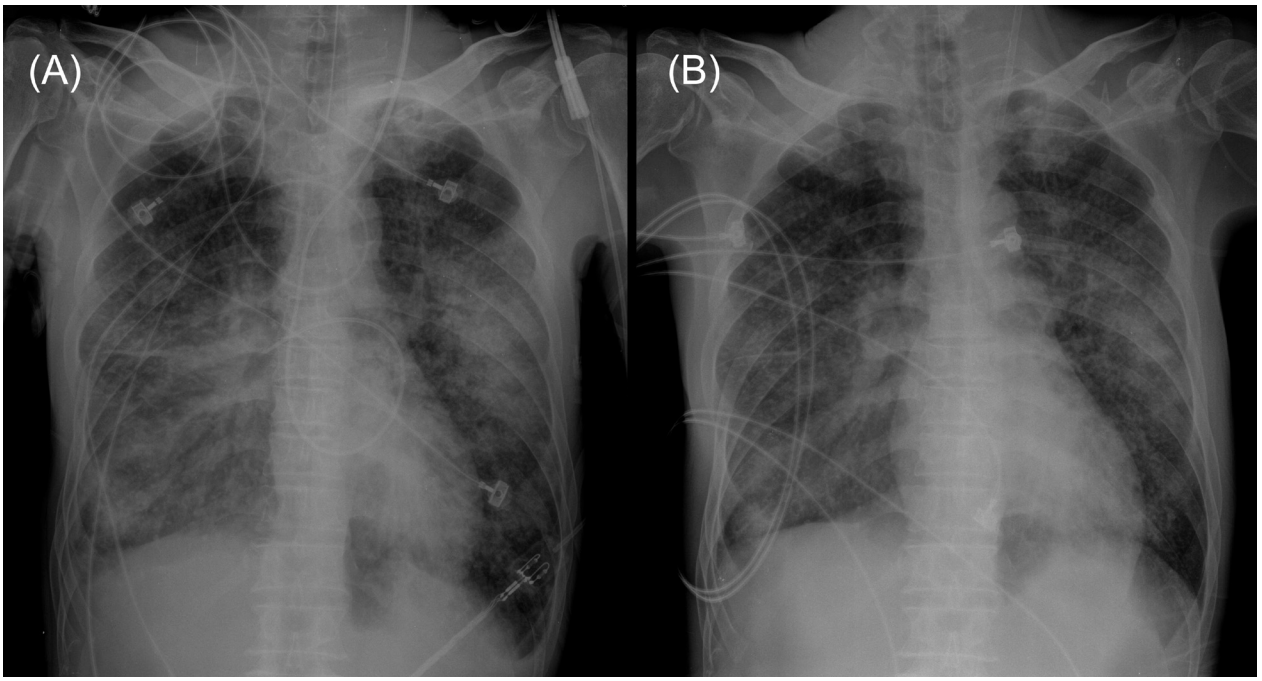

Fig. 1. (A) Chest radiograph showing bilateral alveolar infiltration with diffuse micronodules on admission; (B) Chest radiograph showing improvement 2 days after treatment with intravenous immunoglobulin.

raphy revealed a normal systolic function and minimal pericardial effusion, with pulmonary arterial pressure of 26 mmHg. Laboratory microbiological studies, including sputum Gram's stain and culture, blood culture, sputum fungus culture, throat swab for viral isolation, human influenza rapid test, pneumococcal antigen, Widal and Weil-Felix test, serology for leptospirosis, serum Epstein-Barr virus (EBV), viral capsid antigen immunoglobulin M (VCA-IgM), cytomegalovirus (CMV) IgM, herpes simplex virus (HSV) IgM, and blood and sputum PCR for pneumocytic pneumonia, all showed negative results. Atypical pneumonia for chlamydia, mycoplasma and legionella, hepatitis C virus antibody (anti-HCV), hepatitis B surface antigen, and antibody to human immunodeficiency virus (anti-HIV) also revealed negative results. Autoimmune screening tests including ANA (anti-nuclear antibody), rheumatoid factor, complements, and immunoglobulin levels, were negative, as well. A very high level of ferritin (10,308 ng/ml) was noted on day 2 of admission. Bone marrow aspiration biopsy was performed on day 4 of admission on suspicion of HPS, and showed CD-68-positive reactive macrophages with phagocytosed myeloid cells, without increased blast cells (Figure 2). Due to the patient's deteriorating condition, intravenous immunoglobulin (IVIG), at a dose of 1 gm/Kg/day, was used for 2 consecutive days starting from day 4 of admission after confirmation of bone marrow aspiration biopsy. Three sets of sputum acid-fast stain were negative, but tuberculosis polymerase chain reaction (TB-PCR) of sputum was positive. Anti-tuberculous medications with isoniazid, ethambutol and pyrazinamide were initiated with a dose adjust-

ment starting from day 5 of admission. The TB-PCR in the blood was also positive, suggesting disseminated tuberculosis, and sputum mycobacterium culture later revealed *M. tuberculosis*. His hemodynamic status, cytopenia, oxygenation and chest radiography (Figure 1B) improved dramatically. Dopamine was tapered off, and CVVHD was changed to intermittent hemodialysis (HD) on day 2 of IVIG therapy. Although the possibility of combined tuberculosis and other micro-organisms cannot be excluded definitely, tuberculosis was suspected as the most likely organism that triggered HPS, because all serological studies, microbiological cultures of sputum, throat swab, blood, and urine were negative, and there was gradual clinical improvement with anti-tuberculosis therapy, even after discontinuation of antibiotics. The ferritin level declined to 836 ng/ml 3 days after treatment with IVIG. Gradual improvement of urine output was also noted. Rifampicin was also added after the liver transaminase level had returned to normal. He was successfully weaned from the mechanical ventilator after tracheostomy and was discharged from the hospital on day 30 after admission.

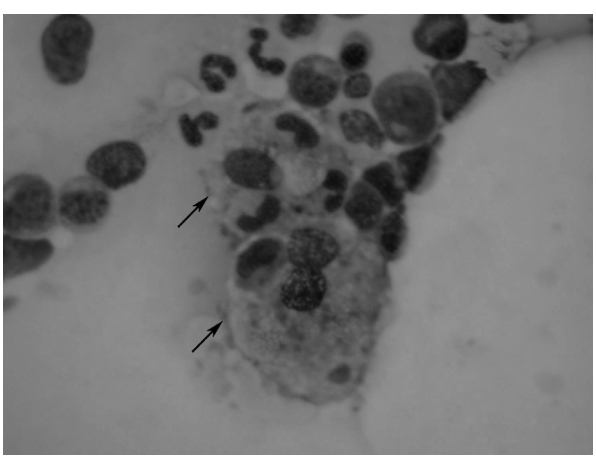

Fig. 2. Bone marrow aspiration biopsy showing macrophages (arrows) with phagocytosed myelocytes (H & E stain 1000X).

Discussion

Hemophagocytic syndrome (HPS) is a reactive disorder of the mononuclear phagocytic system, characterized by benign, generalized histiocytic proliferation, with marked hemophagocytosis [2]. Diagnostic criteria for HPS, proposed by Imashuku, include clinical, laboratory, and histopathologic features: Clinical and laboratory criteria include fever more than 7 days, cytopenia, hyperferritinemia (ferritin ≥ 3 standard deviations (SD) of the normal value or ≥1000 ng/ml), and elevated LDH ≥ 3 SD of the normal value or ≥1000 IU/l. Diagnosis is confirmed histopathologically by hemophagocytosis of activated macrophages in the bone marrow, spleen, or lymph nodes [2].

HPS is classified as familial and reactive, and may be associated with infections (including bacterial, viral, fungal and parasitic), malignancy, or autoimmune diseases [1]. When this syndrome is encountered, it is important to exclude any underlying conditions that may be treatable. Tuberculosis-associated hemophagocytosis is a rare occurrence, but may be life-threatening. It usually develops in immunocompromised hosts [3] or in patients with chronic illnesses, such as cancer, acquired immunodeficiency syndrome (AIDS) [4], diabetes mellitus [5-6], or chronic renal failure [7], and is associated with a mortality rate of about 50%. In our patient, the underlying coal worker pneumoconiosis may have been contributory to the increased risk of tuberculosis.

Although the exact pathogenesis has not yet been clarified, it is suggested that a poorly regulated or inappropriate T-helper 1 (TH1) cell response to intracellular pathogens, with the

production of cytokines, activates macrophages to engulf the blood cells [1]. So HPS is regarded as a cytokine disease or reactive macrophage activation syndrome [2]. It is associated with a high level of tumor necrosis factor (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon-γ [8], and has clinical consequences similar to systemic inflammatory response syndrome (SIRS). The markedly increased level of cytokines (cytokine storm) can lead to multiple organ failure and a life-threatening condition, thus prompt diagnosis is essential. But symptoms of HPS are non-specific, and it is difficult to diagnose at the early stage. It is assumed that HPS is underdiagnosed, and that the cases identified are in a more advanced stage [9].

The serum ferritin level can dramatically increase, more than 10-fold, within hours of the onset of HPS [10]. Ferritin levels >10,000 ng/ml are almost exclusively seen in patients with reactive HPS or adult Still's disease, after excluding diseases like iron overload, human immunodeficiency virus (HIV) infection or AIDS, neoplasia, and fulminant liver cell damage [11]. So the serum ferritin measurement may be used as a simple and rapid screening test for HPS, and a very high level may prompt a high index of suspicion. In our patient, HPS was suspected due to the markedly high serum ferritin level (10,308 ng/ml) without joint symptoms or negative serological tests, and was confirmed by bone marrow aspiration biopsy which showed macrophages with hemophagocytosis without increased blast cells. Moreover, serial measurement of the serum ferritin level in individual patients is closely related to the disease activity [10], as in our case.

Although some case reports have discussed treatment for secondary HPS, including steroid [12], plasma exchange to reduce the plasma cytokines [8], and IVIG [10, 13], apart from the treatment of the underlying disease there is no standard treatment for reactive HPS up to now. Some authors have assumed that IVIG therapy may be beneficial in treating patients with secondary HPS during the early stage [10]. Measurement of serum ferritin levels may be helpful in the early detection of HPS, and lead to the prompt administration of IVIG treatment. Early treatment, especially within 2 days of the ferritin peak, improves the outcome [14]. The mechanism of action is assumed to be competitive binding of the transfused monomeric IgG to the macrophage Fc-receptor (FcR), causing an alteration of macrophage functioning and an anti-inflammatory effect [15]. In our case, the hemodynamic status, oxygenation, cytopenia and chest radiograph improved dramatically after administration of intravenous immunoglobulin for 2 consecutive days. Although there is a controversy over the treatment of secondary HPS, we assumed that a short course of IVIG therapy might play a crucial role in the life-threatening condition by suppressing the cytokine storm. The contribution of steroid in treating HPS cannot be excluded entirely, but the time discrepancy between the administration of steroid and clinical improvement suggested it is unlikely that steroid played an important role [12].

In conclusion, HPS is an uncommon but severe fatal illness associated with a variety of infectious agents, as well as genetic, neoplastic, and autoimmune diseases. Tuberculosis should be taken into account in the differential diagnosis of HPS, especially in tuberculosis endemic areas. HPS may be suspected in patients with very high levels of serum ferritin (>10,000 ng/ml), and intravenous immunoglobulin treatment may improve the outcome in patients with life-threatening HPS during the early phase of the

disease.

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一位瀰漫性結核併嗜血症候群及多重器官衰竭病患接受靜脈注射免疫球蛋白治療的經驗

吳福平　蘇文麟*　彭萬誠*　陳健文*

嗜血症候群是一種罕見但可能致命的疾病。臨床上以不明熱，肝脾腫大，血球低下等方式表現。其病因與感染，遺傳，腫瘤，和自體免疫有關。嚴重嗜血症候群患者也會出現休克，急性呼吸窘迫症候群，以及多重器官衰竭等情形。

本文描述一位重症患者於臨床上診斷出嗜血症候群後，連續接受靜脈注射免疫球蛋白治療兩日而成功改善其血流動脈學與呼吸狀態。後經系列檢查後發現痰液及血液之結核菌聚合酶連鎖反應（polymerase chain reaction）為陽性，痰液之結核菌培養亦為陽性。病患在接受抗結核藥物治療三週後成功拔除氣管內管。結核感染於結核病盛行區應列入嗜血症候群的鑑別診斷，短期使用靜脈注射免疫球蛋白有助穩定此類重症病患之病況。*(胸腔醫學* ***2009; 24: 20-26)***

關鍵詞：嗜血症候群，靜脈注射免疫球蛋白治療，結核

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Epithelioid Hemangioendothelioma, a Rare Tumor of the Mediastinum: Case Report and Review of the Literature

Pei-Sung Hsu*, Yei-San Hsieh**, Diana Yu-Wang Yeh*,***, Jiunn-Song Jiang*,***

Epithelioid hemangioendothelioma (EHE) is a rare low-grade malignant tumor of vascular origin, rarely seen in the mediastinum. We described a 27-year-old male with the initial presentation of cough and hoarseness. A superior mediastinal tumor encasing major vessels with vocal cord and diaphragm paralysis was found on CT scan. He received a wide local resection and the pathology was EHE with malignant histopathologic characteristics. He underwent post-operative adjuvant chemoradiotherapy, but metastases to the pleura and lung developed 3 months later. He then underwent another debulking surgery and photodynamic therapy to control the pleural metastasis. No recurrence or metastasis was found up to the writing of this manuscript.

This case shows that malignant histopathologic features are a major factor determining a poor prognosis, as the tumor is more likely to behave like angiosarcoma. There is as yet no reported case of EHE treated by photodynamic therapy in the available medical literature. Short-term results seemed to be excellent in our index patient. Long-term results will require further study. ***(Thorac Med 2009; 24: 27-35)***

Key words: epithelioid hemangioendothelioma

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare tumor of vascular origin which can be found in many organs. The mediastinum is an infrequent location for this tumor, compared with other sites in the body. EHE behaves like a tumor, and its malignant potential is intermediate, somewhere between benign hemangioma and malignant angiosarcoma [1]. It often presents with local symptoms or as an incidental finding on radiographic study. It is also a rare cause of mediastinal tumor without definitive, curative treatment [2]. Metastasis of mediastinal EHE after radiotherapy or chemotherapy has been reported in a few cases [3-4]. We report an anterior mediastinal hemangioendothelioma in a 27-year-old male with the initial presentation

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of cough and hoarseness. A review of the literature on this subject follows.

Case Report

A 27-year-old male presented with intermittent dry cough for 3 months and subsequent development of hoarseness. He was treated for an upper respiratory tract infection initially, but with no improvement. He was a non-smoker and had no remarkable past medical history.

He was afebrile on presentation, and the physical examination was unremarkable except for superficial vein engorgement noted on the anterior chest wall. Other routine laboratory examinations were within normal limits. The chest X-ray revealed left diaphragmatic elevation and a mild hazy density in the left upper mediastinum (Figure 1). Bronchoscopy identified left vocal cord palsy. A chest computed tomography (CT) scan was done on the suspicion of left laryngeal recurrent nerve and phrenic nerve palsy, and revealed soft tissue density at the left upper anterior mediastinum encasing the great vessels (Figure 2). The positron emission tomography (PET) scan revealed a mild hypermetabolic lesion in the left perithyroid to left retroclavicular region, probably originating in the superior mediastinum with thoracic extension (Figure 3). The uptake intensity value was maximal SUVbw = 3.9-5.5. The possible interpretations of the PET scan included an inflammatory process, benign tumor, and low-grade malignancy. No other hypermetabolic lesions were seen on the PET scan.

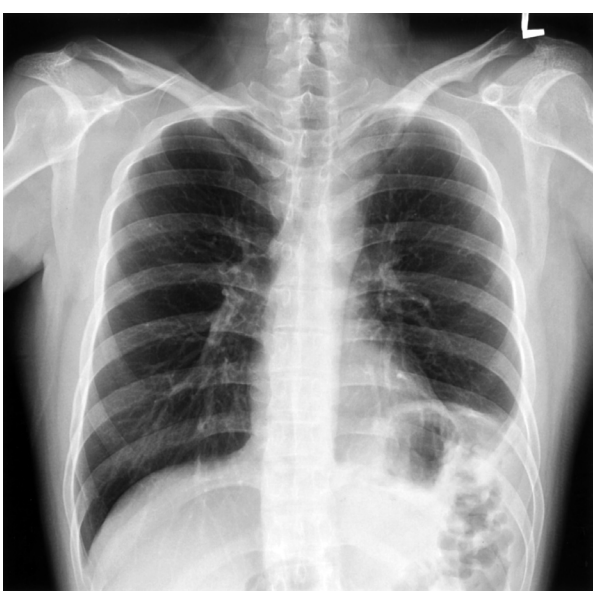
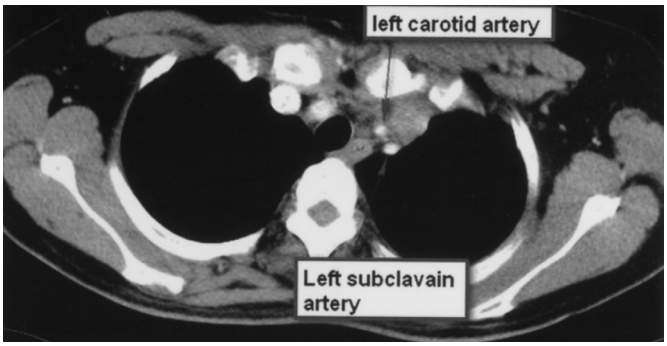


Fig. 1. Chest X-ray revealed left diaphragmatic elevation and a mild hazy density in the left upper mediastinum with cervicothoracic signs.

An extensive resection of the mediastinal tumor was done, and revealed a 2 × 2 cm firm tumor beneath the clavicle, tightly adhering to the internal jugular vein, left carotid artery, left subclavian artery and left recurrent laryngeal nerve. The tumor was dissected from the vessels and removed carefully. The left recurrent laryngeal nerve could not be separated from the tumor.

The tumor had ill-defined margins, measuring 2.0 × 1.5 × 1.0 cm in size. It was tan and firm with a fibrous to hyalinized cut surface, and was composed of epithelioid cells and some spindle cells. The epithelial cells had uniform ovoid nuclei with clear to eosinophilic cytoplasm. Some of them showed intracytoplasmic vacuoles with mild to moderate nuclear atypia (Figure 4). The epithelial cells formed small nests and diffuse sheets; however, there were no obvious mitoses. Small foci of chondromyxoid matrices in the stroma were noted, and focal necrosis was also seen. The tumor had infiltrated into the adjacent fat and skeletal muscle fibers (Figure 5). Immunohistochemical studies with CD31 and Friend leukemia integration 1 (FLI1) revealed reactivity in the tumor cells. The final pathologic diagnosis was EHE. The patient re-



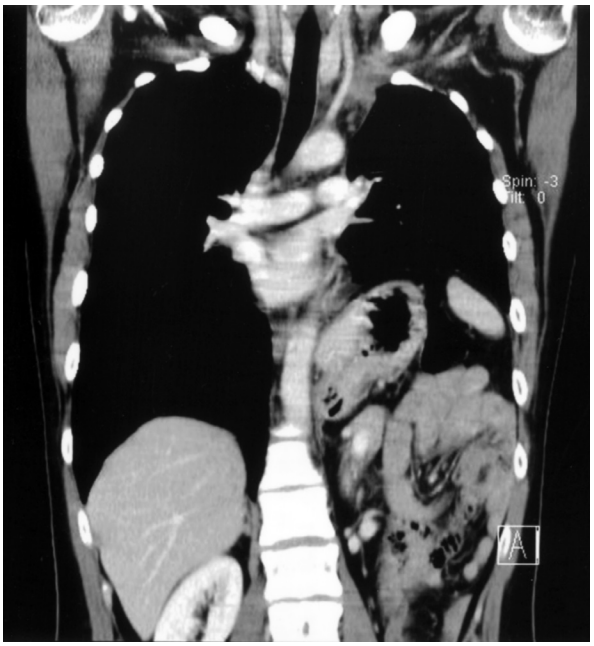


Fig. 2. The chest CT scan revealed soft tissue density at the left upper anterior mediastinum encasing the left carotid artery, phrenic nerve and left subclavian artery.

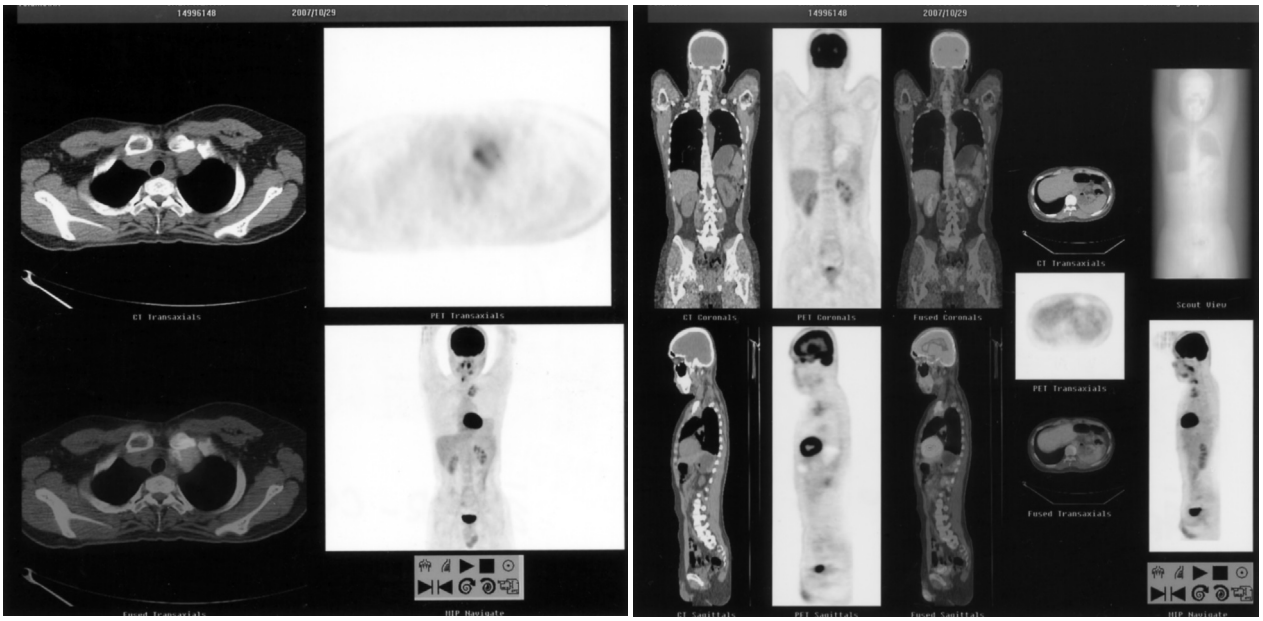


Fig. 3. The PET scan revealed a hypermetabolic lesion in the left perithyroid to left retroclavicular region, probably originating in the lower neck with thoracic extension.

ceived post-operative radiotherapy 6600cGy in 33 fractions 1 month after surgery, and 2 courses of chemotherapy with doxorubicine (18 mg/m^2) / cisplatin (30 mg/m^2) 2 months after tumor excision for the inadequate resection margin and the relatively malignant histology. However, the patient gradually developed exertional dyspnea 3 months after surgery. CXR revealed left-side pleural effusion (Figure 6), and chest CT showed a suspicious soft tissue density

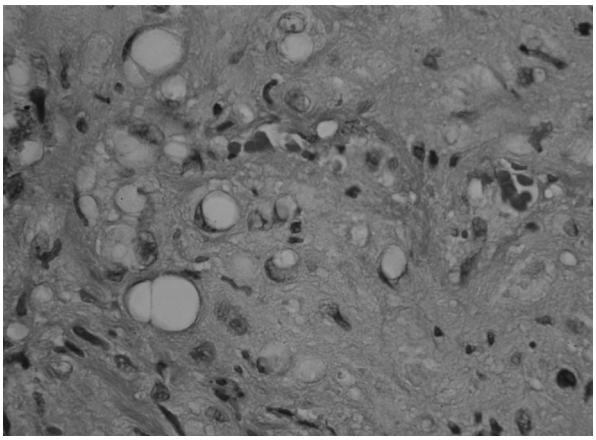


Fig. 4. The epithelial cells had uniform ovoid nuclei with clear to eosinophilic cytoplasm. Some of them showed intracytoplasmic vacuoles with mild to moderate nuclear atypia.

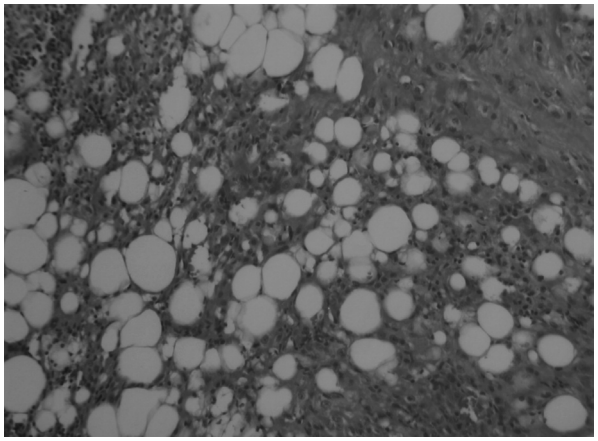


Fig. 5. The tumor infiltrated into the adjacent fat and skeletal muscle fibers.

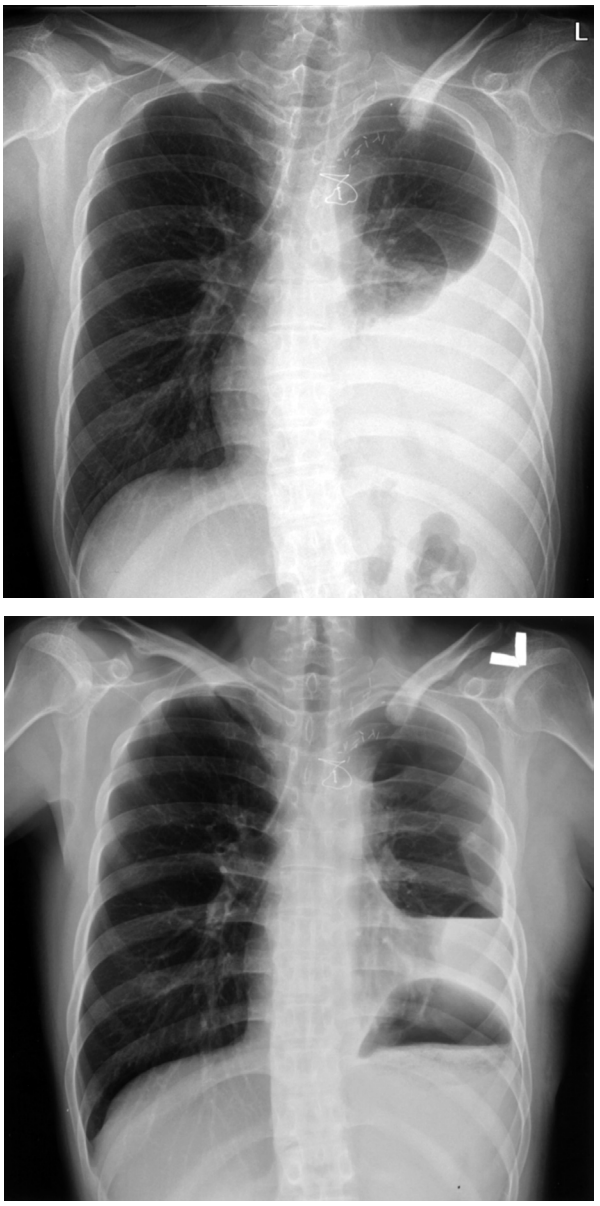


Fig. 6. Three months later, the chest X-ray revealed a large amount of pleural effusion. After debulking surgery and photodynamic therapy for 3 months, the pleural effusion decreased.

with involvement of the anterior chest wall at the left lung apex (Figure 7). This was likely tumor recurrence from the incomplete resection during the first wide local excision. He then underwent video-assisted thoracoscopic surgery, which revealed thickening of both the parietal and visceral pleura and the entrapped left lung. A biopsy of the parietal pleura was done, and revealed metastatic EHE. Due to the pleural metastases, parietal, visceral, diaphragmatic and partial pericardial pleurodectomy and photodynamic therapy were performed through the left pleural cavity. Left upper lung wedge resection was also done, and revealed multiple lung nodules. The above specimens all contained metastatic EHE. The patient was followed regularly up until this point, 3 months after the second operation. A small amount of left pleural effu-

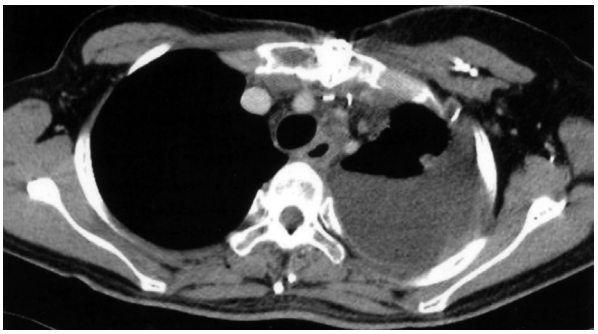


Fig. 7. Suspicious soft tissue density with involvement of the anterior chest wall was noted on the chest CT scan.

sion persisted after operation, but there was no evidence of distal metastasis or recurrence in the gallium tumor scan.

Discussion

In adults, the common causes of anterior superior mediastinal tumors are thymomas, thyroid neoplasms, teratomas and lymphomas. Mesenchymal tumors account for only about 7% of mediastinal tumors [2]. The tumors with a vascular origin are a relatively rare group of mesenchymal tumors in the mediastinum. EHE is a rare tumor within this group, and behaves like a tumor with intermediate malignant potential, somewhere between benign hemangioma and malignant angiosarcoma [1]. The term was first introduced by Weiss and Enzinger in 1982. EHE has been reported to occur in patients with a wide range of ages, and may present in many organs, including the bone, lung, liver and soft tissues. Sometimes, locations such as the CNS, breast or lymph nodes can be involved [5]. Soft tissue is the most common site [1]. More than half of soft tissue EHEs arise from blood vessels such as medium- or large-sized veins, including femoral, iliac or jugular veins [1]. In most cases, EHE only involves a single organ [9]. Multiple organ involvement may be the result of metastasis or a naturally multicentric pattern [1].

In the histopathology, the tumors are composed of cords, short strands or solid nests of rounded to slightly spindle-shaped eosinophilic endothelial cells which have been referred to as "epithelioid" or "histiocytoid." Intracellular vacuoles are common and may have a signet-ring appearance. The cells appear relatively bland with few or no mitotic counts. The intercellular stroma has a chondroid, hyaline, mucinous or myxomatous matrix. Metaplastic bone is occasionally seen. Immunochemical stain identifies a variety of vascular antigens within EHE. Among these antigens, CD31, CD34 and FLI1 are more reliable and sensitive markers than von Willebrand factors. For the treatment of soft tissue EHE, Weiss and Enzinger recommended that if the patient had histological characteristics implicating a relatively poor prognosis, such as increased mitoses, tumor necrosis, cytological atypia or invasive border, more aggressive treatment would be indicated, including radical resection with possible adjuvant chemotherapy [1].

The clinical features of mediastinal EHE vary depending on the location and structural involvement of the tumor, and include cough, chest pain, shortness of breath, dysphagia, vocal cord palsy and superior vena cava syndrome. Sometimes the tumors are asymptomatic and are discovered as incidental radiographic findings. They present as well-circumscribed mass lesions in most cases and may result in mediastinal widening on chest X-ray. On chest CT, they are seen as a mass with variant density. The CT scan often shows the tumor encroaching on major vascular structures. Focal calcifications have been described in some cases [10].

The PET scan is another tool for the evaluation of EHE. Rest *et al*. described a patient with mediastinal EHE with bone marrow involvement who received serial evaluation by PET scan at the time of diagnosis and after completion of radiotherapy and chemotherapy. The increased uptake demonstrated on the PET scan decreased after treatment with radiotherapy and chemotherapy. It is useful in determining the extent of disease and evaluating the response to therapy, and can be reliable even in a patient whose CT scan shows stable disease [4]. The PET scan of our patient before the operation showed no metastasis. A definitive diagnosis of EHE requires histological examination and immunochemical study.

Treatment experience with EHE is limited due to the low incidence of this disease. Surgery is recommended in most cases. Radiotherapy and chemotherapy are used in some cases with metastasis or multicentric lesions, but there is a lack of convincing responses [1, 3-4].

In the case of soft tissue EHE, the metastasis and mortality rates are about 31% and 13%, respectively. In comparing the histological "malignant" form and "benign form", the mortality rates have been reported to be 31% and 3%, respectively [5]. Mediastinal EHEs were less likely to be associated with metastasis or multicentric lesions in a currently available report [10]. One case with liver metastasis and 1 with bone marrow involvement have been reported, and the 2 patients failed adjuvant chemotherapy and radiotherapy [3-4]. Despite the fact that EHE exhibits intermediate malignant behavior, most cases with single organ involvement in the mediastinum showed no recurrence after surgical resection [1, 12].

This patient initially presented with hoarseness and left diaphragm elevation, which indicated left recurrent laryngeal nerve and phrenic nerve palsy due to mediastinal tumor invasion. The chest CT findings were non-specific and difficult to differentiate from other mediastinal tumors. The PET scan revealed a mild hypermetabolic lesion with a maximal SUV of about 3.9-5.5. Generally, the cut-off value of maximal SUV for malignancy is around 2.5. Therefore, the PET scan suggested the possibility of a low-grade malignancy in this case. During the initial resection, the observation that the tumor adhered tightly to the great vessels served as a hint that a tumor of vascular origin should be among the differential diagnoses. Microscopic findings of epithelioid cells forming small nests, intracellular vacuoles, and positive immunohistochemical staining of vascular antigens CD31 and FLI1 were compatible with the histopathologic features of EHE. The findings of mild to moderate nuclear atypia, focal necrosis and invasive borders pointed to a more malignant form of EHE with the higher metastasis and mortality rates reported in a previous study [1].

Pleural and lung metastases occurred 3 months after surgery despite adjuvant chemoradiation. Although the initial PET scan did not show involvement of other sites, a small metastasis could have been difficult to detect. As the initial wide local excision operation did not enter the pleural cavity, the possibility of intraoperative pleural seeding was low. These considerations meant that our patient had rapid progressive disease, despite surgical resection and aggressive chemoradiotherapy.

The second chest CT revealed a soft tissue density at the left lung apex. This indicated likely tumor recurrence arising from incomplete resection of the tumor during the first operation. However, the previous literature reported several patients who, despite receiving incomplete

surgical resection, had no recurrence or metastasis for more than 2 years after surgery [10-11, 14]. Early metastasis or recurrence is less common in mediastinal EHE, as seen in the few available case reports. We know, however, that this patient differed from previously reported patients in that his tumor had malignant histopathologic features, such as mild to moderate nuclei atypia and focal necrosis, and infiltration to the adjacent fat and skeletal muscle. These histopathologic features were similar to malignant angiosarcoma and probably made this malignant form of EHE behave more like angiosarcoma with a higher metastatic potential, and consequently, a poorer prognosis. We believe this was the principle factor contributing to the early metastasis and rapid progression in this patient.

We performed surgical debulking and photodynamic therapy for the pleural and lung metastasis. In a previous phase II study, photodynamic therapy was shown to be effective in decreasing local recurrences of pleural metastasis in some selected patients [15]. Our patient received a gallium tumor scan 3 months after debulking surgery and photodynamic therapy for pleural metastasis, which showed no evidence of recurrence or new metastasis. This represents adequate local control by photodynamic therapy for the 3-month observation period. The patient will continue to be followed to evaluate the benefit of photodynamic therapy. To our knowledge, this is the first time photodynamic therapy has been utilized to treat pleural metastases of EHE.

Conclusion

EHE is a rare tumor of the mediastinum. It should be kept in mind as a differential diagnosis if the mediastinal tumor encases great vessels. It is usually a low-grade malignant tumor and is treated in most cases by radical resection only. If more malignant histopathologic characteristics are noted, however, the patient should receive aggressive chemoradiotherapy, as the tumor would likely have a higher metastasis rate, similar to angiosarcoma, and a poorer prognosis.

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罕見的縱隔腔腫瘤“類上皮性血管內皮瘤”：病例報告

徐培菘* 謝義山** 葉育雯*,*** 江俊松*,***

類上皮性血管內皮瘤是一種罕見的血管低惡性腫瘤，少見於縱膈腔。我們提出一位27歲男性一開始以咳嗽及聲音沙啞表現。胸部電腦斷層顯示一上縱膈腔腫瘤包圍著大血管，導致聲帶及橫膈麻痺。他接受手術切除而病理報告顯示類上皮性血管內皮瘤併有惡性病理特徵。術後並接受化學放射治療。但是3個月後發現肺部及肋膜轉移。他接著接受切除手術及光動力刀治療來控制肋膜轉移。目前沒有發現局部復發或轉移。

這個病例顯示出惡性的病理組織特徵是決定這個病預後的主要因素。有這樣的惡性的病理組織特徵會使得腫瘤表現的像惡性的血管肉瘤。光動力刀治療類上皮性血管內皮瘤併肋膜轉移的方式在文獻上尚未被報導，短期的效果良好，但長期的效果有待進一步追蹤。*(胸腔醫學* ***2009; 24: 27-35)***

關鍵詞：類上皮性血管內皮瘤

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Pulmonary and Peritoneal Tuberculosis with Tubercular Splenic Abscess

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Splenic abscess is uncommon, with an incidence of 0.14% to 0.7% in autopsy-based studies. The most common pathogen of splenic abscess in Taiwan is *Klebsiella pneumoniae*; *Mycobacterium tuberculosis* is very rare as a causative agent in an immunocompetent patient.

We report a 76-year-old woman with active pulmonary tuberculosis who presented with left upper quadrant abdominal pain associated with fever for several days. Computerized tomography scan of the abdomen revealed multiple low density wedge-shaped lesions in the upper and lower portions of the spleen. Tubercular splenic abscess was confirmed by histopathological examination of the excised spleen. Pulmonary tuberculosis was diagnosed via positive sputum acid-fast smear and culture.

Tubercular splenic abscess should be on the list of differential diagnoses of an active pulmonary TB patient who presents with left upper quadrant pain and fever. Early anti-tuberculosis treatment should be started and splenectomy reserved for those with an unsatisfactory response or complications, so as to prevent mortality. ***(Thorac Med 2009; 24: 36-41)***

Key words: tubercular splenic abscess

Introduction

Extrapulmonary tuberculosis can occur in isolation or along with pulmonary TB. Extrapulmonary TB constitutes 15% to 20% of all cases of TB in immunocompetent patients and accounts for more than 50% of cases in human immunodeficiency virus (HIV)-positive patients [1].

Splenic abscess is uncommon, with an incidence of 0.14% to 0.7% in autopsy-based studies [2]. The most common pathogen of splenic abscess in Taiwan is *Klebsiella pneumoniae* (*K. pneumoniae*); *Mycobacterium tuberculosis* (*M. tuberculosis*) is very rare as a causative agent in immunocompetent patients [3-4]. We report a case of active pulmonary TB combined simultaneously with tubercular splenic abscess.

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Case Report

A 76-year-old Taiwanese woman, a lifetime nonsmoker, was referred to our hospital by a primary care physician, due to left upper quadrant abdominal pain and intermittent fever for 2 weeks. She also had mild productive cough and poor appetite. She denied alcohol intake or illicit drug consumption. She had a history of normal pressure hydrocephalus and had received a ventriculoperitoneal shunt several years ago.

On physical examination, her body temperature was 38.9°C, pulse rate: 108/minute, respiratory rate: 24/minute, and blood pressure: 132/80 mmHg. She had icteric sclera and pale conjunctiva. Crackles were audible in the bilateral lung field. Abdominal examination revealed an enlarged spleen with tenderness and shifting dullness. There was no muscle guarding, rebounding pain, or positive Murphy's sign.

Hemogram showed normocytic anemia, thrombocytopenia, and monocytosis without leukocytosis (hemoglobin: 10.2 g/dL, platelets: 32,000/μL, white cell count: 6400/μL, neutrophils: 51%, lymphocytes: 17% and monocytes: 30%). Abnormal serum biochemical results included total and direct bilirubin, which was 2.49 mg/dL and 1.64 mg/dL, respectively. Bone marrow study was performed for thrombocytopenia and showed nonspecific changes. Two sets of blood culture yielded no growth.

Chest radiography revealed increased bilateral interstitial infiltrates, bilateral pleural effusion and plate-like atelectasis in the right lower lobe (Figure 1). Abdominal ultrasonography showed multiple hypodense lesions within the spleen and a small amount of ascites. Lymphocyte-predominant exudative ascites was found after paracentesis. Abdominal computerized tomography (CT) scanning showed ascites and splenomegaly with multiple splenic infarctions or splenic abscess (Figure 2). The differential diagnosis by imaging findings included splenic lymphoma, metastasis, abscess, hamartoma, and granulomatous inflammation, such as sar-

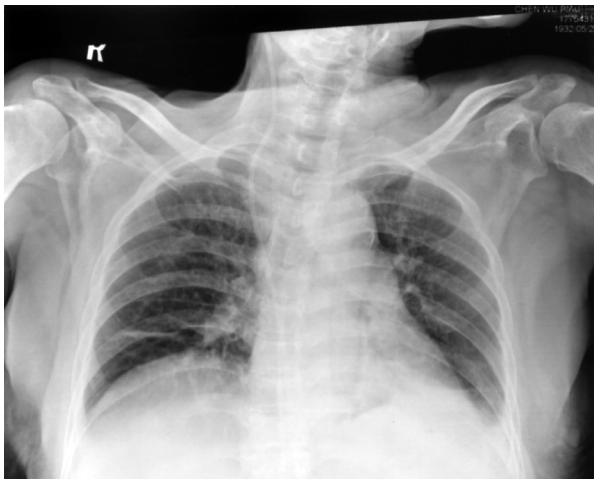

Fig. 1. Chest radiography showed interstitial infiltrates in both lung fields, plate-like atelectasis in the RLL, and bilateral pleural effusion. There was no evident fibrotic change in either upper lung field.

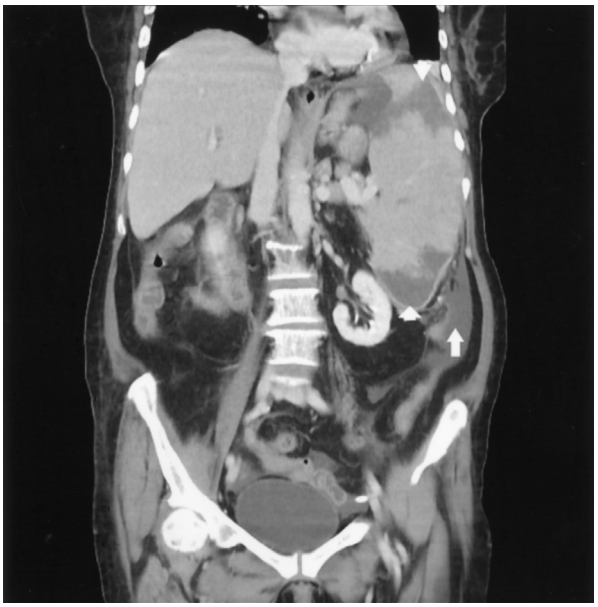

Fig. 2. Coronary reformatted image of an enhanced abdominal CT scan showed wedge-shaped low density lesions in upper and lower portions of the spleen (arrow heads). Ascites was found in the peritoneum, especially near the spleen (arrow).

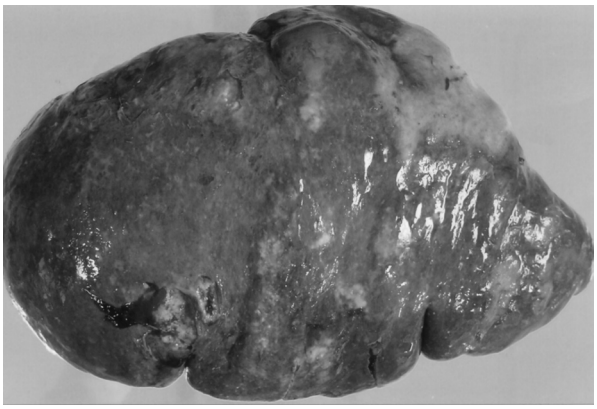

Fig. 3. Congestion with fibrous adhesions and yellow abscess formation demonstrated in the spleen.

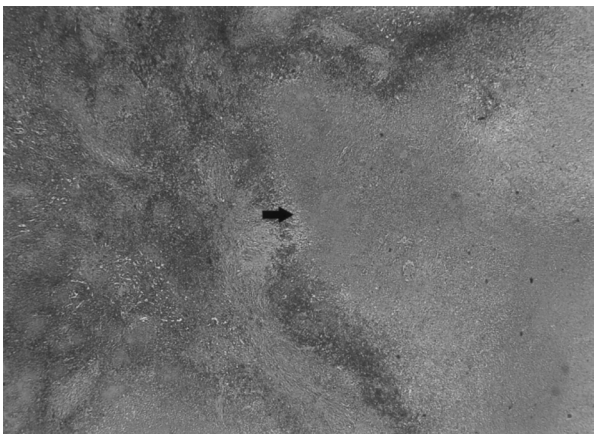

Fig. 4. Section of spleen demonstrates caseous necrosis (arrow) (Original magnification X40)

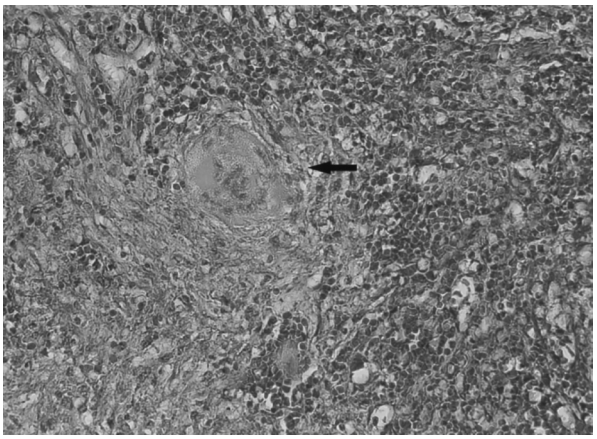

Fig. 5. Epithelioid histiocytes, lymphocytes and Langhans giant cells (arrow) are presented (Original magnification X400)

coidosis, TB or fungal infection [5-8]. Echocardiography was arranged to rule out the infective endocarditis that causes splenic abscess, and the result was unremarkable.

Exploratory laparotomy showed that the spleen was enlarged (22.5 × 15 × 7 cm, 1080 gm) and congested, with fibrous adhesions and yellow abscess formation (Figure 3). Histopathological examination showed caseous necrosis with Langhans giant cells (Figures 4, 5), and Ziehl-Neelsen staining revealed acid-fast bacilli. The bacteria, fungal and mycobacterial cultures of the abscess were all negative. During hospitalization, pulmonary TB was diagnosed by positive sputum acid-fast smear and isolation of *M. tuberculosis* from the sputum.

The patient began daily anti-tuberculous regimens with isoniazid, rifampicin, pyrazinamide and ethambutol. Testing for antibodies to HIV was negative. Later, ascites culture also yielded *M. tuberculosis* complex. Susceptibility tests of the *M. tuberculosis* isolates showed sensitivity to all first-line anti-tuberculous drugs.

Thus, pulmonary TB with tubercular splenic abscess and peritoneal TB was diagnosed. After splenectomy and anti-tuberculous therapy, the patient's abdominal pain resolved and the abnormal hemogram, including monocytosis and thrombocytopenia, improved. However, the low-grade fever persisted and the patient expired due to ventilator-associated pneumonia 1 week after operation.

Discussion

Splenic TB is a rare form of extrapulmonary TB. The most frequent extrapulmonary sites of TB were the lymphatic system, pleura, and osteoarticular and other sites [1]. Extrapul-

monary TB accounted for 10.3% of all TB cases in Taiwan in a 1997 report, in which the pleura was the most commonly involved site and gastrointestinal TB comprised only 1.5% of extrapulmonary TB [9]. Sputum acid-fast stain and mycobacterial culture should be performed for every case of extrapulmonary TB, as suggested by Taiwan's CDC. The chest radiography of our patient was not typical of pulmonary TB, yet *M. tuberculosis* was isolated from the sputum. This fact indicates the necessity of sputum acid fast stain and mycobacterial culture in patients with extrapulmonary TB.

Fever, abdominal pain and tenderness confined to the left upper quadrant are the main symptoms of splenic abscess [3]. In addition, left pleural effusion was present in 19% to 22% of patients with splenic abscess [10-12]. Underlying conditions that predispose patients to the development of splenic abscess include diabetes mellitus, malignancy, trauma, intravenous substance abuse, immunosuppression therapy and HIV infection. The most common cause of splenic abscess is septic embolism, and endocarditis is frequently the source of septic emboli [3, 12]. *K. pneumoniae* is the leading pathogen causing splenic abscess in Taiwan, in contrast to other series in which *E. coli* was the most prevalent [3, 10-12]; *M. tuberculosis* is extremely rare as a causative agent in an immunocompetent patients. Splenic abscess due to *M. tuberculosis* is mostly diagnosed in immunocompromised or miliary TB patients [13-15].

The best diagnostic methods for tubercular splenic abscess are abdominal CT scanning and sonography, which often reveal round or ovoid, single or multiple, low density lesions. The CT number is around +35~+45 Hounsfield units (HU) [5-8]. Definite diagnosis relies on a demonstration of characteristic histological changes with acid-fast bacilli and/or isolation of *M. tuberculosis* from the spleen. The very low incidence of tubercular splenic abscess in the literature may be due to the infrequent use of splenic biopsy for pathologic study or mycobacterial culture. The most common complication of splenic abscess is peritonitis, because of its rupture into the peritoneal cavity. Our patient's peritoneal TB may have been secondary to this complication.

Four-combined anti-tuberculous therapy for the initial 2 months, followed by 3-combined therapy, is the standard treatment of extrapulmonary TB. Whether splenectomy is necessary for tubercular splenic abscess is still controversial due to the lack of a randomized controlled trial. Medical treatment alone has been successful in some patients [16-17]. Splenectomy may be performed if the response to medical treatment is not satisfactory or intractable complications such as splenic rupture or uncontrollable bleeding occur [18-19]. Splenomegaly in patients with TB may result in a variety of hematologic abnormalities, including pancytopenia, myelodysplasia and polycythemia vera [20].

In conclusion, in a patient with pulmonary TB, left upper quadrant pain and fever, tubercular splenic abscess should be placed in the list of differential diagnoses. Early anti-tuberculous treatment should be started and splenectomy reserved for any unsatisfactory response or complication, so as to prevent mortality.

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肺及腹膜結核合併結核性脾膿瘍

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脾膿瘍是種罕見的疾病，以病理解剖的研究顯示發生率約在0.14%到0.7%。在臺灣造成脾膿瘍最常見的病原菌是克雷伯氏菌，因結核菌造成脾膿瘍更為稀少，大部份發生在免疫不全的病患上。

我們報告一個76歲女性，症狀為左上腹痛及發燒數天，其腹部電腦斷層發現許多脾化膿的區域，利用脾臟切除及病理切片得到結核性脾膿瘍的診斷。同時利用痰液及腹水的耐酸性染色及培養證實患者有活動性肺結核及結核性腹膜炎。

在一位活動性肺結核的病患身上，如果發現有發燒及左上腹疼痛時，結核性脾膿瘍是必需列入的診斷選項。抗結核藥必需及早給予，脾臟切除則保留在病患對藥物反應不良時施行。*(胸腔醫學* ***2009; 24: 36-41)***

關鍵詞：結核性脾膿瘍

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Synchronous Double Primary Malignancy: Adenocarcinoma of Lung and High-Grade Brain Malignancy, Anaplastic Oligoastrocytoma

Yung-Yuan Lin, Ching-Hsiung Lin, Chin-Shui Yeh, Chun-Chi Chang, Ying-Ming Shih, Shang-Yun Ho*, Wei-Liang Chen*, Tsung-Han Teng**

Synchronous double primary malignancy of the lung and brain is extremely rare, as there were only 2 cases reported in the literature. If patients were found to have both lung and brain malignancy, they would be ordinarily be considered to have lung cancer with brain metastasis.

We report a 76-year-old female who came to our hospital due to slurred speech for 2 weeks. Brain magnetic resonance imaging (MRI) showed a heterogeneous mass lesion at the left parietal lobe with perifocal edema. Stereotactic biopsy confirmed anaplastic oligoastrocytoma. In the meantime, the pre-operative chest radiograph accidentally found a patch of opacity at the left hilar area during the same admission. The chest computed tomography (CT) scan showed a mass lesion at the left lingular lobe; bronchoscopic finding was unremarkable. Histology of the CT-guided biopsy specimen showed adenocarcinoma. Due to the poor performance status and the patient's family refusing operation, only palliative radiotherapy to the brain was administered. She was still living 7 months later.

This case report highlights the importance of searching for and confirming synchronous tumor in addition to lung cancer, since there is the potential of cure and long-term survival. ***(Thorac Med 2009; 24: 42-48)***

Key words: synchronous double primary malignancy

Introduction

Among cancer patients, 1% to 2.6% may have another primary malignancy. This has been called multiple primary neoplasms [1-2]. About one-third of multiple primary neoplasm patients were synchronous, and the others were metachronous [1]. We defined synchronous as the second neoplasm occurring less than 6 months after the first cancer was found [1, 3].

In the initial diagnosis of lung cancer, 12% to 18% of patients may have brain metastasis [4]. If lung cancer patients have a brain tumor, simultaneously metastasis will be considered in most cases. But occasionally, double primary tumors of the lung and brain may be found syn-

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chronously. We present a case of synchronous primary brain and lung malignancy diagnosed at the same time.

Case Report

A 76-year-old female housewife, a lifetime non-smoker, was referred to our hospital due to slurred speech for 2 weeks. She had had hypertension and coronary artery disease for decades, both treated with regular medication. She denied any traumatic event or exposure to industrial dust or chemicals. On physical examination, her temperature was 36.5°C, blood pressure was 108/70 mmHg, and pulse rate was 76 beats per minute. Examination of the lungs, heart, and abdomen was unremarkable. Neurologic examination revealed mild right-side extremity muscle weakness and unstable gait. Cranial nerve function was intact. Her hemoglobulin was 9.9 g/dL without leukocytosis. Biochemistry showed only hypokalemia 2.9 mEq/L.

We arranged a brain CT scan first, due to the suspicion of an acute cerebrovascular accident or intracranial lesion. A mass-like lesion in the left brain was seen. Primary brain tumor was highly suspected, but metastasis could not be ruled out. We scheduled a brain MRI for a more detailed tumor image study, and it showed a heterogeneous mass lesion at the left parietal lobe 4.8 × 5.1 × 6.8 cm in size that involving both gray and white matter (Figure 1). The pathology report of the stereotactic biopsy confirmed anaplastic oligoastrocytoma (Figure 2).

At the same time, pre-operative routine chest radiography showed a patch of opacity at the left hilar area (Figure 3). Chest CT scan showed a 3.25 cm mass lesion at the left lingular lobe without mediastinal or hilar lymph node enlargement. Bronchoscopic findings were unremarkable. Adenocarcinoma was diagnosed after CT-guided biopsy (Figure 4). The clinical staging of the left lung cancer was T2N0M0, stage1B.

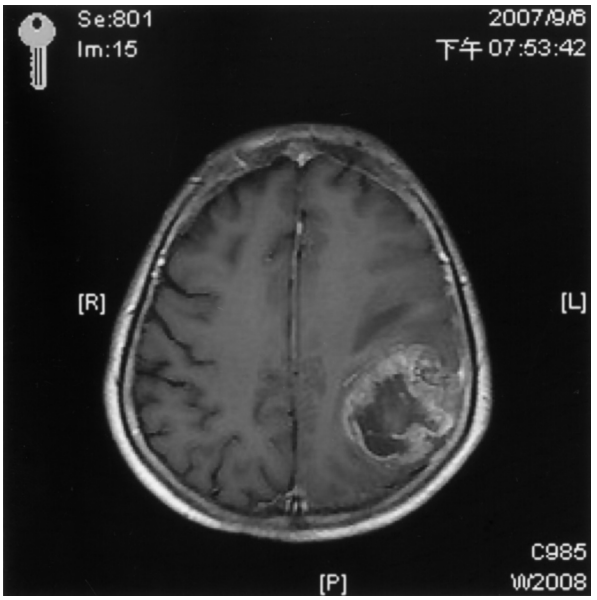

Fig. 1. Brain MRI showing a large lobulated mass in the left temporoparietal lobes with perifocal edema.

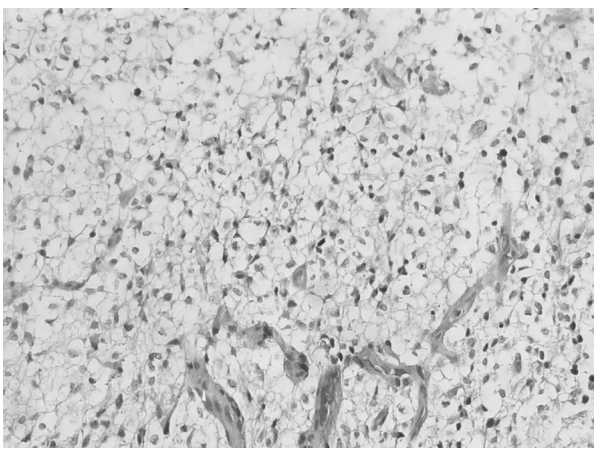

Fig. 2. Section demonstrates oligodendroglial and astrocytic differentiation. Nuclear atypia, cellular pleomorphism and high cellularity are presented, compatible with anaplastic oligoastrocytoma.

Operations for both the brain and lung tumor were suggested. The lung cancer operation would be arranged after the brain surgery, depending on the patient's general condition. Ow-

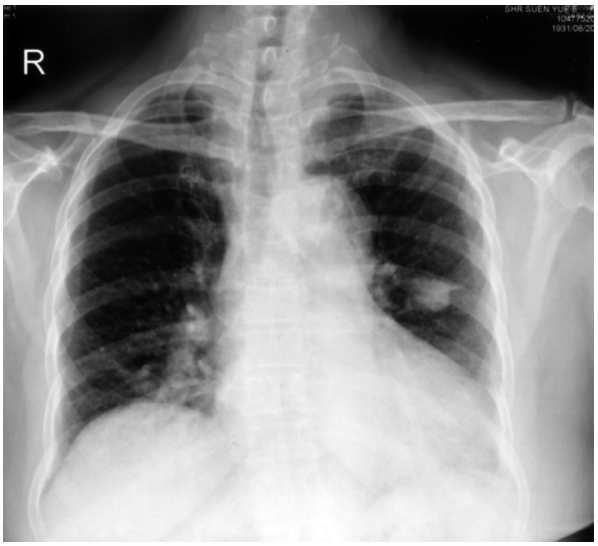

Fig. 3. Posterio-anterior chest X-ray showing a patchy lesion with relatively clear margin in the left lung.

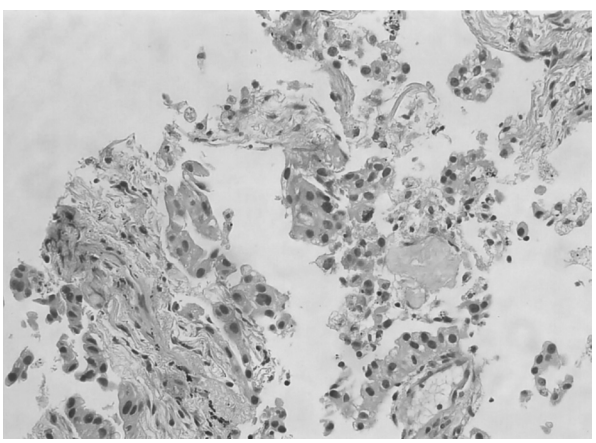

Fig. 4. CT-guided lung biopsy shows the presence of atypical glandular structures with minimal stromal invasion in the limited stroma tissue. The stroma shows desmoplasic change with lymphocytic infiltrates and fibrosis. Focal reactive type II pneumocytes are also demonstrated. The pathologic diagnosis was adenocarcinoma.

ing to the patient's advanced age and poor performance status, her family refused these operations. Only palliative radiotherapy to relieve the neurological symptoms was administered. The patient was still alive 7 months later.

Discussion

In the initial diagnosis, 12-18% of lung cancer patients had brain metastasis [4]; furthermore, 75.4% of brain metastatic tumors came from the lung [5]. There have been only 2 cases of synchronous lung and brain malignancies reported (Table 1). Both of these cases were malignant astrocytoma, grade II brain malignancy, which differs from our patient's grade III (high grade) brain malignancy [6].

There are 2 categories of "synchronous": (1) cancers occuring at the same time, and (2) within 2, 6, or 12 months of each other [1, 7-8]. The survival of patients with synchronous tumors, in 1 study, was significantly lower then that of patients with malignancies of a metachronous nature (61.3% vs. 69.9% in 1-year survival and 11.9% vs. 26.0% in 5-year survival) [9]. We reviewed 21 reports, including 519 cases of synchronous double primary malignancies associated with the lung that occured within 6 months (Table 2). The most common site of the second primary malignancy, in addition to lung cancer, was the digestive tract. The 3 leading areas were the stomach (28.3%), esophagus (9.8%) and colon (7.5%). However, the number of double primary lung and brain malignancies was zero in the largest case report, which included 465 patients [10]. We found that those patients whose disease was operable had a better prognosis than the inoperable patients. The most common synchronous tumor sites along with the lung were the digestive tract, especially the stomach, followed by the larynx and prostate.

Are there any factors related to synchronous lung and brain tumor? Recent studies showed that a codeletion of 1p/19q is highly associated with glioma; however, only 14-20% of anaplastic oligoastrocytoma patients had this gene dele-

Table 1. Previous reports of synchronous double primary malignancy of the lung and brain

Year	Authors	Age	Gender	Lung cancer	Brain tumor	Exposure history	Survival	Treatment
2008	Lin YY	76	F	Adeno	Anaplastic oligoastrocytoma	Nil	>7m	R/T
1992	Kishimoto T [16]	54	M	BAC	Malignant astrocytoma	Asbestos 8 years	3m	nil
1989	Hashimoto H [13]	54	M	BAC	Malignant astrocytoma	-	-	-*

BAC, bronchioloalveolar carcinoma; Adeno, adenocarcinoma; R/T, radiotherapy

* only English abstract, article in Japanese

Table 2. Literature review of synchronous lung cancer and primary tumors at other sites

Year	Case number	Author	Lung cancer	Primary tumor at other site	Tx	Prognosis	
2008	1	Lin YY	Ade	Brain	R/T	>7 m	
2007	1	Sarkar S	NSCLC	Testis	C/T	3wk	[17]*
2003	1	Tamura K	BAC	Ampulla vater	OP**	>5 yr	[18]
2001	1	Eriguchi N	-	Ampulla vater	-	-	[19]
2000	2	Eriguchi N	NM	Pancreas	-	4-13 m	[20]
1999	465	Kaneka S	-	Stomach	-	-	[10]
1998	1	Nosaka S	SCC	Sigmoid colon	OP	>1 yr	[21]
	4	Nosaka S	Ade	Stomach	OP	>1 yr	
1998	1	Morio A	Ade	Stomach	OP	NM	[22]
1996	1	Tsuji K	Ade	Colon	OP	NM	[23]
1996	1	Nosaka S	SCC	Sigmoid	OP	NM	[24]
	1	Nosaka S	Ade	Stomach	OP	NM	
1995	1	Shimada J	-	Stomach	OP	NM	[25]
1995	1	Kantardzic	-	Bladder	-	-	[26]
1993	21	Fekete F	-	Esophagus	-	-	[27]
1992	1	Fukaura A	SCC	CLL	Nil	-	[28]
1992	1	Kishimoto T	BAC	Brain	Nil	3 m	[16]
1991	1	Morimoto M	Ade	Esophagus	OP	>22 M	[29]
1990	1	Libby DM	Ade	Kidney	OP	>1 yr.	[30]
1990	1	Fukuda H	SCC	Esophagus	OP	>25 M	[31]
1989	1	Hashimoto H	BAC	Brain	-	NM	[13]
1984	3	Arimura T	-	Stomach	OP	NM	[32]
1983	2	Vyas JJ	Ade	Larynx, Palate	-	-	[33]

R/T, radiotherapy; C/T, chemotherapy; OP, operation ;NSCLC, non-small cell lung cancer; Ade, adenocarcinoma; BAC bronchioloalveolar carcinoma; SCC, squamous cell carcinoma; CLL, chronic lymphocytic leukemia; NM, not mentioned

* reference.

**OP: op in this table indicates both malignancies were surgically resected

tion, which was lower than that for other histological types of glioma [11]. One report described multiple cancers in families associated with a germline P53 mutation [12]. Asbestos exposure was considered to possibly be the responsible carcinogen in the second patient in Table 1 [13]. However, we did not trace a significant asbestos exposure history in our patient.

Standard treatment for malignant gliomas consists of resection, when feasible, and radiation [14]. Some recent studies suggested chemotherapy with a PCV regimen (procarbazine, CCNU, vincristine) or temozolomide (TMZ) for recurrent oligodendroglial tumors [11]. However, treatment protocols vary, depending on the histological subtype of glioma. Thus, treatment strategies in cases of synchronous double malignancy depend on treating the malignancy that is more advanced first, or sometimes treating them simultaneously [15]. Because of advanced age, this patient decided to undergo palliative radiotherapy only to the brain, and was alive 7 months after treatment. Moreover, aggressive treatment, such as operation for synchronous primary cancer, if feasible, might be the best method to increase survival in this patient group [18, 21, 29-31].

In conclusion, this case report highlights the importance of searching for and confirming a synchronous tumor in addition to lung cancer, because there is the possibility of curing the double primary malignancy, with resultant long-term survival. In patients who have lung cancer, the possibility of a synchronous secondary primary tumor always has to be considered. Since gastrointestinal cancer is the most common secondary site, in addition to lung cancer, physicians need to be alert to abdominal symptoms such as poor appetite, dysphagia or bowel habit change in screening tests for secondary cancer.

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同時發生的二處惡性腫瘤：肺腺癌和腦部的分化不良型寡樹突星狀膠質細胞瘤

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同時在腦部及肺部發現原發惡性腫瘤是非常少見的，文獻中只有2個病例報告。由於病例稀少，當一個病人被診斷肺癌，而腦部又發現有另一個腫瘤的話，大部分的病人會被當成肺癌併腦轉移。

我們報告一個76歲女性，她因為講話含糊不清持續二週而到我們的醫院就診。腦部核磁共振檢查發現左邊頂葉有一個腫瘤，腫瘤周圍並有水腫。接著安排病人接受立體定位切片，病理診斷為分化不良型寡樹突星狀膠質細胞瘤（anaplastic oligoastrocytoma）。同一時間，手術前的例行性胸部X光片檢查意外發現在左肺門區域有一個濃度增加的病灶，胸部斷層掃瞄顯示是一個腫瘤在左肺舌葉。支氣管鏡檢查並無異常發現，而斷層掃瞄導引下切片證實了是肺腺癌。由於患者年紀較大及活動力差，家屬拒絕手術及化學治療，病人僅接受緩解症狀的腦部放射治療，病人目前已存活超過7個月。

這個病例提醒我們，去尋找並診斷和肺癌同時發生的另一個惡性腫瘤是很重要的；因為這二個腫瘤都有可能治癒，而病人可能獲得長時間的存活。*(胸腔醫學* ***2009; 24: 42-48)***

關鍵詞：同時發生的二處原發惡性腫瘤

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Boerhaave's Syndrome – A Case Report

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Spontaneous perforation of the thoracic esophagus, known as Boerhaave's syndrome, develops after vomiting or retching due to massive alcohol or food ingestion. An uncoordinated esophageal sphincter reflex opening results in a sudden increase of intramural esophageal pressure and complete transmural rupture in the weakest region, which is often the left lateral wall of the distal esophagus. This causes mediastinitis, empyema, sepsis and multi-organ failure, accounting for a mortality ranging from 20% to 40%. The prognosis depends on the interval from onset to management and the underlying physical status of the patient. Urgent surgical intervention within 24 hours after onset is advocated. Primary repair of the esophageal perforation and drainage of the pleural contamination should be done if conditions are feasible. Enteral nutrition should be reestablished by gastrostomy or jejunostomy.

We reported a case of Boerhaave's syndrome. Urgent surgical intervention was undertaken immediately after diagnosis, within 24 hours after onset. Primary repair of the esophageal perforation was successful. Oral feeding started on postoperative day 33 and no complications occurred after a 4-month follow-up. In such cases, an early and accurate diagnosis, timely surgical intervention, infection control and nutritional support in the postoperative period will lead to a better prognosis. ***(Thorac Med 2009; 24: 49-53)***

Key words: Boerhaave's syndrome, esophageal perforation

Introduction

Spontaneous perforation of the thoracic esophagus, Boerhaave's syndrome, is the most serious cause of esophageal perforation. It can cause mediastinitis, empyema and sepsis, and accounts for a mortality rate ranging from 20% to 40% [1]. The non-specific initial symptoms often make an accurate diagnosis difficult, and a delay of management usually leads to a poor prognosis. Herein, we report a case of Boerhaave's syndrome successfully managed by surgical intervention; no complications occurred after a 4-month follow-up.

Case Report

A 68-year-old male, an alcohol drinker, had a history of hypertension without regular medical control, and coronary artery disease with a triple-vessel disease status post-coronary artery bypass graft. A sudden onset of post-emetic

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chest pain with radiation to the left shoulder occurred after drinking alcohol. Aortic dissection was suspected initially at a local hospital. At our emergency department, tachypnea, tachycardia, fever and left chest pain were noted. Lab data revealed leukocytosis, an elevated CRP level, and normal cardiac enzyme. Computed tomography (CT) scan of the chest disclosed bilateral pleural effusion, pneumomediastinum and distal esophageal perforation (Figure 1). Under the impression of spontaneous esophageal perforation, an emergency surgery was undertaken about 22 hours after the development of symptoms. A left exploratory thoracotomy revealed a 3 cm linear transmural perforation just above the esophagogastric junction and on the left posterior wall of the distal thoracic esophagus (Figure 2). After debridement of the mediastinal abscess, primary repair of the esophageal perforation with coverage by the surrounding mediastinal pleura was performed. In addition, decompressive gastrostomy and feeding jejunostomy were also performed by laparotomy. The postoperative course was smooth and oral feeding started on postoperative day 33, without leakage. No complication occurred after a 4-month follow-up.

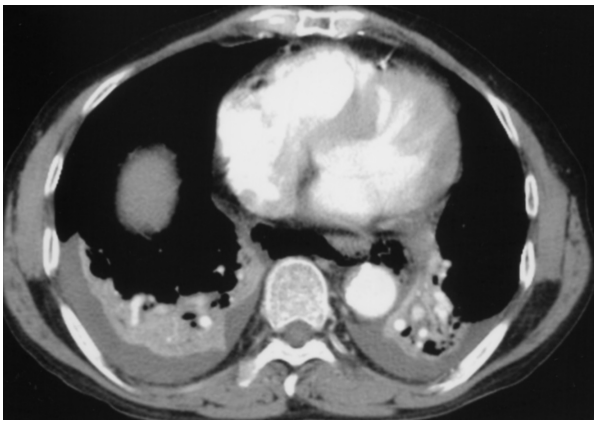

Fig. 1. The computed tomography scan of the chest revealed bilateral pleural effusion, pneumomediastinum and a perforated distal esophagus, which extended into the left pleural cavity.

Fig. 2. Using a left thoracotomy, a 3 cm linear transmural perforation in the left posterior wall of the distal esophagus was found. The extent of pleural contamination was limited.

Discussion

Spontaneous perforation of the thoracic esophagus, Boerhaave's syndrome, was first described in 1724 by Herman Boerhaave [2]. Vomiting or retching due to alcoholism or excessive food intake leads to an uncoordinated esophageal sphincter reflex opening and results in a sudden increase of intramural esophageal pressure, causing complete transmural rupture in the weakest region, which is often the left lateral wall of the distal esophagus [3]. Due to the toxic potential of micro-organisms in the gastrointestinal tract, and digestive activity with gastric, pancreatic or hepatic juice, this condition can result in mediastinitis, empyema, sepsis, and multi-organ failure, and accounts for a mortality ranging from 20% to 40%. The classic triad of symptoms includes retching, sudden epigastric pain and shock. However, the initial symptoms are usually non-specific and mimic myocardial infarction, pericarditis, acute pancreatitis, pneumothorax, or perforated peptic ulcer [4]. Therefore, delay of diagnosis and treatment leads to a

poor prognosis.

Successful management of this disease depends on a timely, accurate diagnosis and an appropriate choice of treatment. A detailed history-taking and physical examination are important. Image studies, including chest plain film, CT scan of the chest and contrast esophagography, and diagnostic tapping of pleural effusion can be helpful in confirming the diagnosis [5]. The prognosis depends on the interval between onset and management, and the underlying physical status of the patient [6]. Generally, urgent surgical management by direct repair of the esophageal perforation is advocated within 24 hours of presentation, and esophageal exclusion or non-operative management is indicated after 24 hours [7]. The surgical procedure is selected according to the extent of esophageal perforation and the degree of pleural contamination. Primary repair and wide drainage of the mediastinum, as possible, are recommended as standard treatment [8]. Diversion of saliva and gastric juice by nasogastric tube or gastrostomy can also be considered, based on the intra- and postoperative condition. Enteral nutrition by gastrostomy or jejunostomy is also important in the postoperative period [9]. In addition, non-operative conservative treatment could be considered in selected cases. The selection criteria that had been reported included disruption contained in the mediastinum, cavity draining back to the esophagus, and minimal symptoms and signs of sepsis [10].

In this case, the diagnosis was quickly established and the esophageal perforation that extended into the left pleural cavity was significant. Therefore urgent surgical intervention was undertaken within 24 hours of onset. Primary repair of the esophageal perforation and drainage of the pleural contamination were performed successfully. Diversion procedures for the gastrointestinal fluid proximal and distal to the perforation, using a nasogastric tube and gastrostomy, respectively, were also applied, accompanied with jejunostomy as an enteral feeding route. Although postoperative empyema developed, which was controlled by prompt antibiotics, oral feeding started on postoperative day 33 and no esophageal leakage was noted.

In conclusion, spontaneous esophageal perforation, Boerhaave's syndrome, should be appropriately managed immediately after diagnosis. Urgent surgical intervention is recommended within 24 hours of onset and the surgical procedure should be selected individually, based on the extent of perforation and mediastinitis. The prognosis depends on a timely and accurate diagnosis, and the selection of management.

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Boerhaave 氏症候群——病例報告

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自發性食道破裂（Boerhaave氏症候群）發生於酗酒或大量進食後嘔吐病人，起因於食道括約肌不協調收縮導致食道腔內壓急遽上升，造成食道下段破裂，通常發生於左後壁，常引起嚴重之縱膈腔炎，膿胸，敗血症，甚至多重器官衰竭，死亡率可高達20-40%。此症之預後與發生至治療的時間長短，以及病患身體狀況相關，一般建議於發生後24小時內進行外科手術，在情況許可下應直接修補食道破裂處及引流胸腔內污染物，同時以胃或小腸造廔作為腸道營養之途徑。

我們報告一位68歲病例，於發生24小時內實行食道修補，胸腔內引流，減壓性胃造廔及灌食性小腸造廔，病患術後恢復良好，於術後第33日開始經口進食，至今追蹤四個月亦無併發症發生。針對此症病患，及時且正確之診斷，於發生24小時內進行手術修補破裂處，術後持續感染控制及給予腸道營養補充，將有較佳之預後。*(胸腔醫學* ***2009; 24: 49-53)***

關鍵詞：食道破裂，Boerhaave氏症候群

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Mediastinum Chordoma: A Case Report

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Chordoma is a slow-growing yet locally aggressive malignant neoplasm of the bone derived from remnants of the embryonic notochord. Thoracic chordoma is even rarer. It may occur at the skull base (35%), at the cervical, thoracic and lumbar spine (2.3-15%), and at the sacral regions (50%). We present a 21 year-old girl who had a slow-growing left-side mediastinal tumor for 14 years. The chest X-ray film showed a benign-looking, small-sized, well-circumscribed tumor with calcification; the benign appearance on the chest X-ray delayed her prompt diagnosis and treatment.

The patient began to experience left hand dryness 2 years previously, and a recent onset of back pain. Echo-guided aspiration revealed cords and lobules of large tumor cells in the chondroid stroma. Immunohistochemical staining was positive for S-100 protein, cytokeratin and vimentin. These observations indicated a malignant chordoma. She received a total surgical resection of the tumor, together with a partial osteotomy of C7 and T1-T3. The area of bone substance loss was filled with cement. Adjuvant stereotatic radiotherapy with 50 Gy was given. No local recurrence was seen after 5 months. ***(Thorac Med 2009; 24: 54-59)***

Key words: mediastinum chordoma

Introduction

Chordoma is a rarely reported and slow-growing malignant neoplasm presumed to be derived from the remnants of the embryonic notochord along the length of the neuraxis at developmentally active sites, such as the end of the neuraxis and the vertebral bodies [1-3]. Despite current evidence indicating that such tumors contain immuno-phenotypic and ultra-structural markers of epithelial differentiation, they are generally classed among bone tumors because of their frequent association with extensive destruction of bony structures. Chordoma typically presents in adults 40 years of age or older and males are affected more often than females. Symptoms are localized and result from the mass effect of the tumor. The natural history is local recurrence with persistent tumor growth and eventual death from local diseases, or less frequently metastases [4].

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Case Report

We present a 21-year-old girl who had a slow-growing left-side mediastinal tumor for 14 years. She was regularly followed up by a family physician. Because the small-sized, well-circumscribed tumor with focal calcifications exhibited slow growth in the yearly chest X-ray follow-up, no further testing was done. She began to experience left hand dryness 2 years previously. There was no significant abnormal sensation in her left hand, and neither edematous change, nor abnormal skin color was noted. There was also no chest pain, cough, dysphagia or dyspnea noted in the past 2 years. She was referred to Chung Shan Medical School Hospital for further treatment because of the recent onset of back pain in the interscapular area and worsening anhidrosis. A chest X-ray showed widening of the mediastinum (Figure 1). A chest computed tomography (CT) scan revealed a well-defined hypodense mass with calcifications occupying the left posterior mediastinum, measuring 7.5 × 5.3 cm from the spinal level of T1 to T5, extending to the right posterior mediastinum at about 3.59 x 1.63 cm in size at the spinal level of T1 to T3, causing vertebral body erosion from T1 to T3 (Figure 2). There was no definite enhancement of the mass after IV contrast infusion. A bone scan revealed no metastatic lesions.

Echo-guided aspiration was performed after consent was obtained. Histopathologically, the lesion showed lobules and cords of large tumor cells embedded in a chondroid stroma (Figure 3A). Some cells showed nuclear atypia. Almost all of the tumor cells were physaliphorous with some intracellular vacuoles in their cytoplasm (Figure 3B). Neither necrosis nor mitotic features could be identified. The

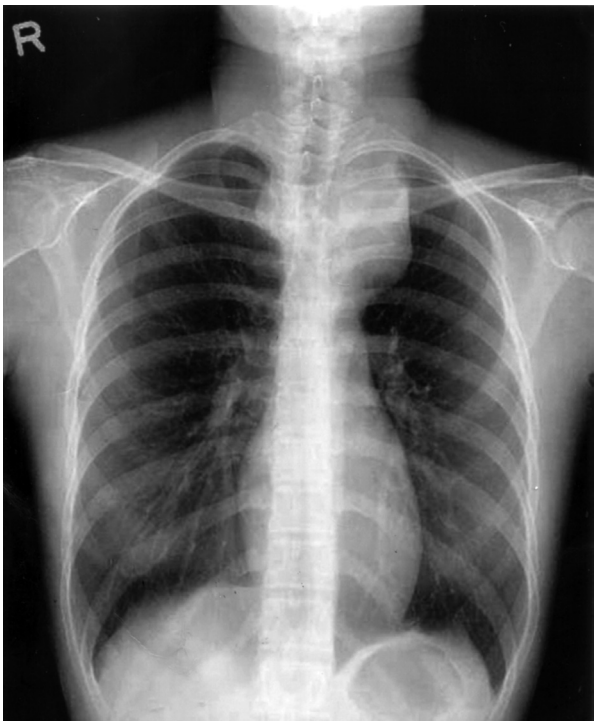

Fig. 1. Chest film showing widening of the mediastinum.

immunohistochemical study showed positive staining of the tumor cells with broad-spectrum keratin (AE1/3) (Figure 3C), S-100 protein and vimentin (Figure 3D). Histopathology and immunohistochemistry were both conclusive to the diagnosis of chondroid chordoma.

The patient received a thoracotomy incision, which extended posterior and superior to the spinous process of C7, and she underwent a total resection of the tumor together with a partial osteotomy of C7 and T1-T3, with the areas of bone substance loss being filled with cement.

After the operation, local adjuvant stereotatic radiotherapy with 50 Gy was performed. Five months later, there was no local recurrence, but the residual symptom of hand anhidrosis persisted. She will have regular follow-ups at 6-month intervals.

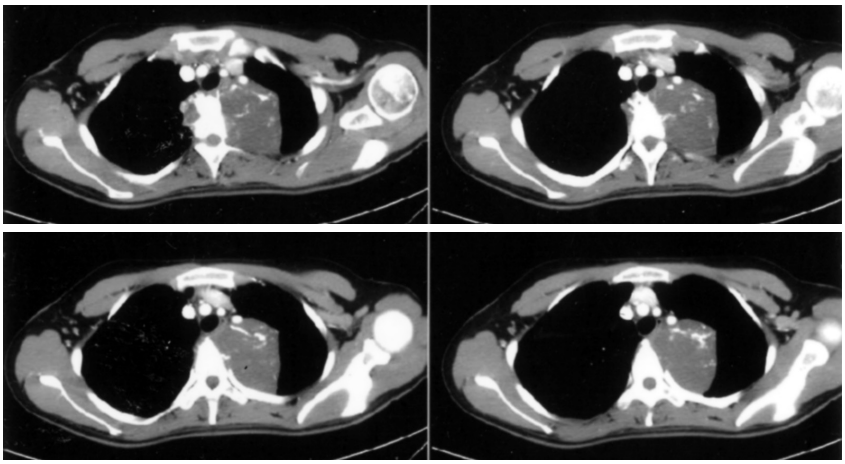

Fig. 2. Chest tomography showing a left posterior mediastinum calcified mass with T1-T3 vertebral body erosion.

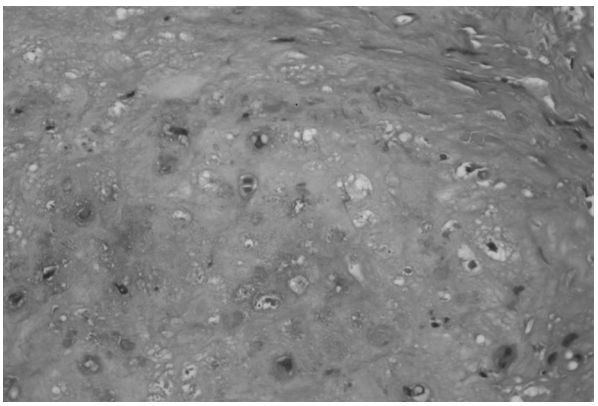

Fig. 3A. Low-powered view of clusters of tumor cells in the chondroid stroma (hematoxyline & eosin stain, X200).

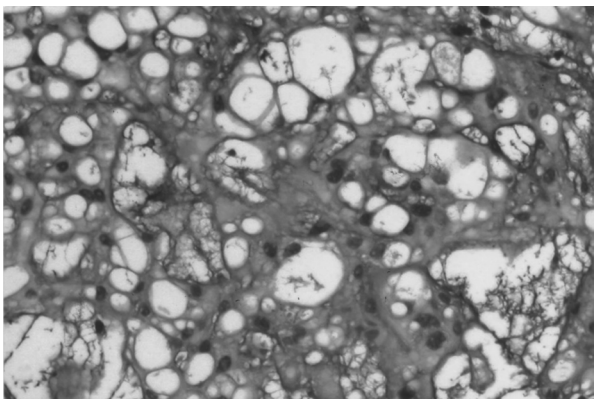

Fig. 3B. Low-powered view of physaliphorous tumor cells with vacuolated cytoplasm (hematoxyline & eosin stain, X400).

Discussion

Chordoma is a rare, slow-growing, locally aggressive neoplasm of the bone. Thoracic chordoma is rarely seen. Its benign appearance on a chest X-ray may delay the en bloc resection of the tumor. A differential diagnosis should be made with chondrosarcoma, mucinous adenocarcinoma, myxopapillary ependymoma, and epithelioid hemangioendothelioma, according to the specific S-100 protein expression, vimentin and cytokeratin stains.

The immunohistochemical staining of chondrosarcoma shows positive for S-100 protein and CD99, and negative for vimentin and cytokeratin stains. Mucinous adenocarcinoma reveals positive staining for vimentin and cytokeratin, but is negative for S-100 protein. Myxopapillary ependymoma is positive for S-100 protein, glial fibrillary acidic protein and CD99, and negative for vimentin and cytokeratin stains. Epithelioid hemangioendothelioma appears

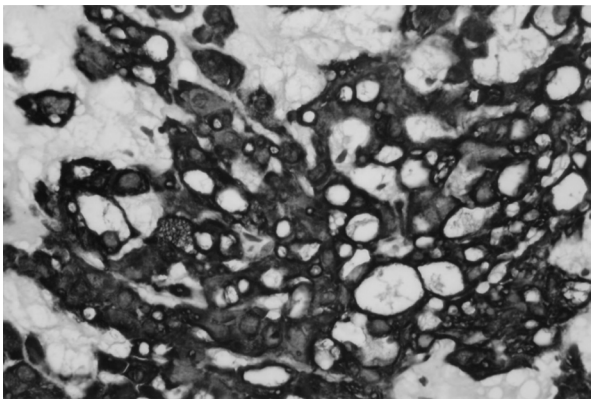

Fig. 3C. The cytoplasm of tumor cells showing strong reactivity (brown color) for cytokeratin (immunohistochemistry, X400).

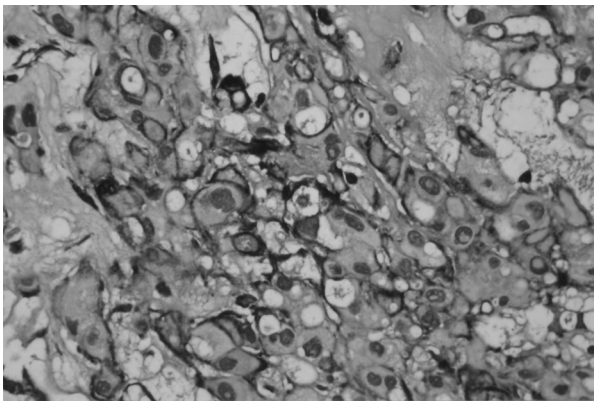

Fig. 3D. The cytoplasm and membranes of the tumor showing mild to moderate reactivity (brown color) for vimentin (immunohistochemistry, X400).

positive for factor VIII-related antigen and vimentin and negative for S-100 protein expression and cytokeratin stains. Immunohistochemical studies of benign chondroma have been reported to have positive staining for CAM 5.2, broad-spectrum keratin, epithelial membrane antigen (EMA) and vimentin, and to a lesser extent, S-100 protein [5]. In addition, stains for muscle actin, carcinoembryonic antigen (CEA), and desmin have been negative.

The clinical presentation depends upon the site of origin and extension of growth. Magnetic resonance imaging (MRI) is the best technique for assessing the extent of tumor, but CT is important for demonstrating local bone destruction.

In less than 10% of cases, chordomas contain sarcomatous or malignant spindle cell features. These undifferentiated chordomas tend to be even more aggressive with early distant metastases [2]. There are no reports of elevated beta-hCG in patients with chordomas, but it is possible that an undifferentiated chordoma with sarcomatous features may produce beta-hCG [2].

Chordoma is 1 of the most challenging of mesenchymal tumors to treat effectively, despite the relatively slow growth rate. The standard therapy is radical resection. High-dose radiation is increasingly used in combination with surgery (for close or positive tumor margins) or alone for nonresectable lesions, especially S1-2 lesions. Local regrowth or metastatic disease may develop after 15 years; in other words, there is a possible disease-free survival rate of 15 years, but not necessarily a cure. Chordoma has a low sensitivity to chemotherapy; aggressive initial therapy improves the overall outcome. Surgery is performed to obtain diagnostic tissue and reduce the tumor burden, which increases the effectiveness of radiotherapy. Conventional photon irradiation appears to result in poor local control in patients with macroscopic residual disease following surgery. The local control rate is dependent upon the volume of residual disease following surgery. Park reported a high local control rate with surgical and radiation treatment of primary lesions (12 of 14), compared to recurrent lesions (1 of 7). Therefore, high-dose proton/photon therapy offers an effective treatment option for primary lesions [6].

Several factors may help predict the survival rate following proton beam irradiation, that is, female sex, skull base chordoma, and larger tumor volume (≥70 ml) may decrease the survival rate. Surgical resection plus post-surgical radiotherapy seems to be the standard treatment for chordoma, but the prognosis for this kind of tumor is unpredictable because of the high recurrence rate (50%). The slow growth, benign appearance, and nearly symptom-free nature lead physicians to ignore the continuing growth and eventual local invasion into the contra-lateral vertebral body. Although our patient received a total resection of the mediastinal chordoma, the symptom of hand anhidrosis remained. Her prognosis would have been much better if a radical resection had been arranged years before. This case study of a rare thoracic chordoma allows us to recommend maintaining an aggressive attitude toward a mediastinal tumor, because a calcified and well-defined tumor could be a malignant chordoma.

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縱隔腔脊索瘤——病例報告

張蒼育　蘇建銘*　楊國坤　吳子卿

脊索瘤是一種緩慢生長，起源於殘餘胚性背索的腫瘤，但是對局部組織破壞性很強，可發生於顱骨底（35%），頸，胸，腰脊椎（2.3-15%），和薦椎（50%）。胸廓的脊索瘤同樣罕見。在此一病例報告中，我們報告一個21歲女性病患，有一個緩慢生長達14年的左側縱隔腔腫瘤。其X光表現像良性的腫瘤，即邊緣清楚，鈣化及生長緩慢，而延遲病患的及時診斷和治療。

她兩年前開始出現左手乾燥的症狀。最近出現胸後背部痛.超音波指引抽吸術病理檢查報告為小葉和圓狀的大腫瘤細胞於軟骨樣基質。特殊免疫染色呈現對S-100蛋白，細胞角蛋白（cytokeratin），波形蛋白（vimentin）陽性。這些檢查證實為惡性脊索瘤，病患隨後接受此縱隔腔腫瘤的完全切除，同時進行C7, T1-T3的局部切骨術及填充骨泥。病患術後接受50Gy局部立體放射線治療，至今5個月也沒有局部復發。
*(胸腔醫學 **2009; 24: 54-59**)*

關鍵詞：縱隔腔脊索瘤

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High-Grade Myxoid Spindle Cell Sarcoma of the Pleura

Wen-Chi Chao, Shen-Yung Wang*, Chao-Hung Chen**, Jian Su, Chien-Liang Wu

Spindle cell sarcomas arise from primitive mesenchymal cells and have a broad spectrum of histological differentiation. They are rare but diversified in presentation, as well as outcomes. A small group of these rare malignant tumors presents spindle cells embedded in an abundant myxoid stromal matrix. The myxoid spindle cell sarcomas mostly involve the extremities, and their occurrence in the pleura is rare. The distinguishing of the various sarcomas within the group of myxoid spindle cell sarcomas is complicated. We report a case of high-grade myxoid spindle cell sarcoma arising from the pleura presenting with massive pleural effusion. Thoracoscopic inspection of the pleural cavity showed a fleshy and gelatinous formless mass. Surgical removal provided only temporary relief. The tumor re-grew rapidly and did not respond to salvage radiotherapy. The histological patterns and the immunohistochemical studies suggested a high-grade myxoid spindle cell sarcoma. However, the features of the tumor presented here were distinct from those of the published differential diagnoses of myxoid spindle cell sarcoma. The literature was reviewed and the differential diagnoses of the presented case explored. ***(Thorac Med 2009; 24: 60-67)***

Key words: myxosarcoma, pleural neoplasms

Introduction

Spindle cell sarcomas belong to a rare group of pleural neoplasms. The tumor cells are derived from primitive mesenchymal cells that are capable of differentiating into a variety of cell types. The resulting histological spectrum of spindle cell sarcomas is broad. A spindle cell sarcoma may present a mixture of features from its subtype along with those of others. Therefore, making a correct diagnosis of a specific spindle cell sarcoma is a formidable task. Myxoid change may be found in most soft tissue tumors. The myxoid substances are glycosaminoglycans, consisting of varied compositions of sulfated proteoglycan and hyaluronic acid. The myxoid matrix is usually limited and is characteristically prominent in myxoid tumors [1]. The myxoid tumors mostly involve the extremities; pleural involvement, however, is scarce and unexpected [1]. We herein report a case with a high-grade myxoid spindle cell sarcoma invading the pleura. The literature was reviewed and the differential diagnoses of this

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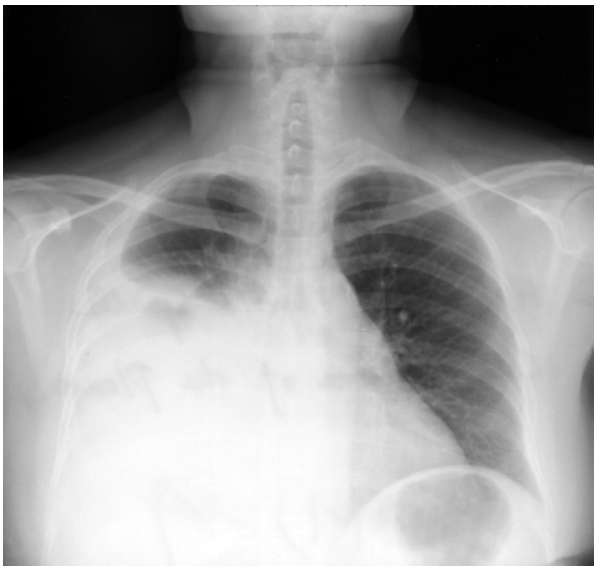
rare disease entity are discussed.

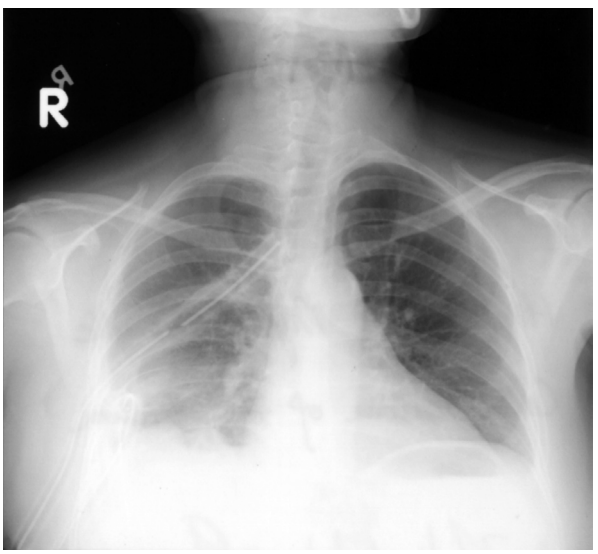
Case Report

A 54-year-old woman presented with cough and progressive exertional dyspnea for 10 days. Adenocarcinoma of the rectum had been diagnosed 2 years prior to this presentation. She underwent a radical resection and adjuvant chemotherapies. In the subsequent follow-ups, there was no evidence of recurrence. There was no known tendency to malignancy in her family. She was a health care worker in a nursing home, and did not smoke or use alcohol. The presenting symptoms were accompanied by scanty white tenacious sputum and dull pain in the lower right chest without fever or hemoptysis. Also, she had a weight loss of 5 kilograms in a course of 6 months.

Physical examination showed dullness to percussion and decreased breathing sounds on auscultation of the right middle to lower chest. A chest radiograph revealed a patch of radiopacity in the right middle to lower lung field, suggesting a massive amount of pleural effusion (Figure 1A). Thoracentesis yielded a serosanguineous, lymphocyte-predominant exudate. The Gram's stain and acid-fast stain of the collected fluid were negative for microorganisms. Malignant cells were not found in the specimen. At admission, laboratory data showed a normal white blood cell count of 8900/mm^3, hemoglobulin of 14.6 g/dL, and a normal biochemical profile. A pigtail thoracostomy had partially drained the pleural effusion for 4 days, and malfunctioned thereafter. Chest computed tomography without contrast enhancement revealed marked right pleural effusion with heterogeneous hypodensities. The contrast-enhanced computed tomography showed several ill-defined hyperdensities distributed irregularly within the pleural cavity (Figure 2). Finally, thoracoscopic inspection of the right pleural space revealed lung entrapment, extensive pleural adhesion, and a massive fleshy, gelatinous structure in the right lower pleural cavity mixed with



(A)



(B)

Fig. 1. The chest radiograph on admission revealed a patch of radiopacity in the right middle to lower lung field (Figure 1A). The lung had expanded after the surgery (Figure 1B).

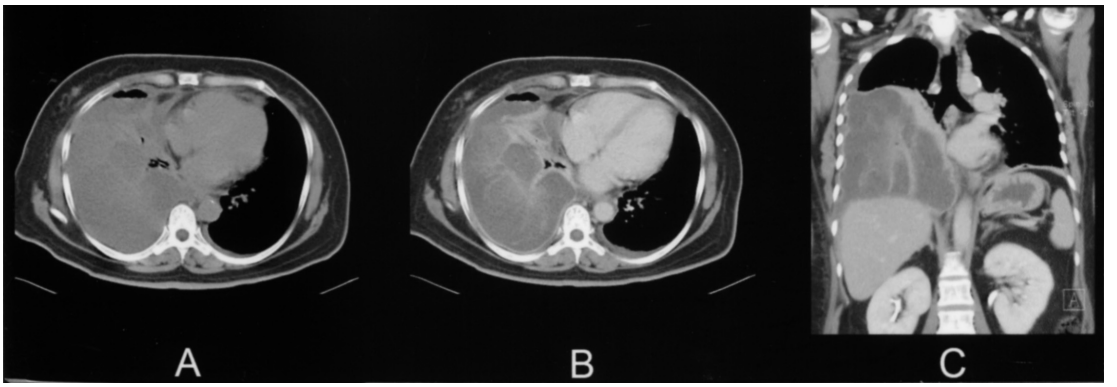
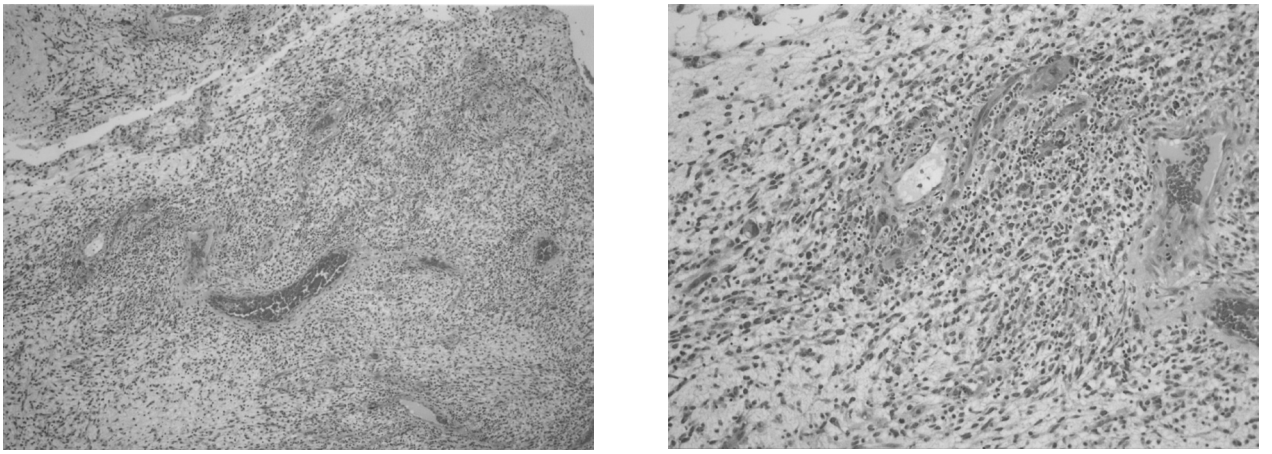


Fig. 2. Chest computed tomography. Non contrast-enhanced axial images revealed marked right pleural effusion with heterogeneous hypodensities (Figure 2A). Contrast-enhanced axial and coronal images showed several ill-defined hyperdensities distributed irregularly within the right pleural cavity (Figure 2B, 2C).



(A) (B)

Fig. 3. The histopathological examination of the pleural tumor revealed disorganized pleomorphic spindle and bizarre giant cells embedded in a myxoid stroma with a thick-walled vasculature (Figure 3A; hematoxylin and eosin stain, 40X). The cellularity is various, and the mitotic figures are numerous, including atypical forms (Figure 3B; hematoxylin and eosin stain, 100X).

hemorrhage. The tumor was removed by thoracoscopy successfully.

The histopathological examination of the specimen revealed disorganized pleomorphic spindle cells and bizarre giant cells embedded in a myxoid stroma with a thick-walled vasculature (Figure 3A). The cellularity varied. Mitotic figures were numerous, including atypical forms (Figure 3B). Immunohistochemically, the tumor cells stained positive for vimentin, cytokeratin, and CD99. Immunostains for desmin, CD34, myoglobin, smooth muscle actin, S-100 protein, calretinin and bcl-2 were negative. Based on these findings, the tumor was diagnosed as high-grade myxoid spindle cell sarcoma. After the surgery (Figure 1B), followed by pleurodesis, the lung had re-expanded and the symptom was relieved. Radiotherapy was planned for the right hemithorax. However, the myxoid tumor had re-grown extensively within

3 weeks and filled the right pleural space, and then tension hydrothorax and respiratory distress developed. The recurrent tumor had a poor response to emergency radiotherapy. Fine needle thoracentesis was performed for decompression, but failed. Surgical decompression was indicated, but her family refused because of the poor prognosis of the disease. The patient deteriorated and expired 2 months after the initial presentation.

Discussion

Spindle cell sarcoma arising from the pleura is rare. A prominent myxoid matrix, comprising glycosaminoglycans in varied compositions of sulfated proteoglycan and hyaluronic acid, is seen in several subgroups of spindle cell sarcoma. The differential diagnoses include myxofibrosarcoma, myxoid liposarcoma, synovial sarcoma, and low-grade fibromyxoid sarcoma. To distinguish between them is challenging; their morphological patterns are similar and cellularity usually varies. Immunohistochemical studies may provide additional information, but they sometimes may be insufficient due to divergence in the differentiation of tumor cells [2]. Therefore, it is crucial to make a diagnosis in conjunction with clinical features, histological patterns, and immunohistochemical studies.

Clinical features are pivotal in differentiating the subtypes of spindle cell sarcoma. Age, sex, and site of involvement are important attributes in classifying these tumors. Myxofibrosarcoma mainly occurs in elderly patients, with a slight male predominance [3]. The majority of these tumors arises from the extremities, but may also be found in unusual locations, such as the head, neck, retroperitoneum, or pleura. The tumor grade is associated with the metastatic potential and prognosis [4]. Low-grade tumors are usually superficial, multiple, and gelatinous. Infiltrative growth patterns with necrosis are usually seen in high-grade tumors. Myxoid liposarcoma occurs generally in young populations, with a peak incidence around the fourth decade. No gender difference is observed. Metastasis is frequently seen, and multiple synchronous or metachronous tumors are not uncommon [5]. Less than a dozen primary pleural myxoid liposarcoma cases have been reported [6]. Low-grade myxoid liposarcoma is usually well defined, but multinodular with a gelatinous cutting surface; high-grade myxoid liposarcoma has more myxoid components with a white fleshy appearance. Synovial sarcoma develops mostly in young people and has a male predominance. This type of sarcoma usually arises from the deep soft tissue of the extremities; however, pleural involvement is rare [7]. Low-grade fibromyxoid sarcoma usually presents as a painless mass of the extremities in a younger population, with the third decade as the median, and with no difference in gender [8]. Distant metastases, especially to the lungs, may eventually develop in a majority of cases.

Histologically, the low-grade area of myxofibrosarcoma has a myxoid-rich matrix. Pseudolipoblasts, the vacuolated fibroblastic cells with a mucin-containing cytoplasm, are frequently seen. The pattern of vascularity is an important diagnostic feature; an elongated and curvilinear vascular pattern is characteristic. The high-grade areas are composed of pleomorphic spindle cells with multinucleated giant cells with abundant eosinophilic cytoplasm. High-grade lesions may intertwine with focally low-grade featured areas [4]. Myxoid liposarcoma comprises primitive non-lipogenic mesenchymal cells and signet-ringed lipoblasts in the myx-

oid stroma [9]. The branching capillaries are thicker than those in myxofibrosarcomas and form a prominent network of "chicken-wire" patterns. The extracellular mucin may make up a "pulmonary edema" growth pattern, which is characteristic [10]. The histological pattern in synovial sarcoma can be biphasic or monophasic. Biphasic synovial sarcomas have varying proportions of epithelial and spindle cell components [11], and monophasic synovial sarcomas usually have pure spindle cell components alone, and mimic other spindle cell tumors [7]. Finally, low-grade fibromyxoid sarcoma is a rare disease that was recently characterized as a distinctive variant of fibrosarcoma [8]. Despite being a malignant neoplasm, the low-grade fibromyxoid sarcoma lacks significant nuclear atypia. The vasculature is different from that of low-grade myxofibrosarcoma and contains small arteriole-sized vessels with peripheral sclerosis [8].

No single immunohistochemical marker has yet been capable of differentiating the spindle cell sarcomas. A panel with diversified markers is usually needed to characterize the type of tumor cells. However, immunohistochemical studies play a small role in diagnosing myxofibrosarcoma and myxoid liposarcoma. The immunoprofile is often used to exclude other types of tumor. Vimentin, a reflection of fibroblastic differentiation, is usually expressed in the spindle-shaped stroma cells in different types of sarcoma. Low-grade fibromyxoid sarcomas typically stain positive for vimentin only and do not express desmin, S100, cytokeratin, or CD34 [8]. Cytokeratin, CD99, and bcl-2 are useful markers in diagnosing synovial sarcoma. A diffuse positivity of cytokeratin in spindle cell tumors is suggestive of sarcomatoid mesothelioma, spindle cell carcinoma, and synovial sarcoma [2]. Most synovial sarcomas demonstrate positive staining of CD99 and bcl-2, especially spindle cells [7, 12].

Our case had a gelatinous tumor emanating from the pleura with pleomorphic spindle cells embedded in a myxoid stroma, which stained positively for vimentin, cytokeratin, and CD99. The tumor showed ubiquitous mitoses with atypical mitotic figures, which is a common feature of high-grade malignancies. These findings were conclusive evidence of a high-grade myxoid spindle cell sarcoma invading the pleura. However, these features differed to various extents from those of published differential diagnoses of myxoid spindle cell sarcoma. It is difficult to conclude that ours was a case of myxofibrosarcoma due to the absence of a characteristic capillary network. Although the typical vasculature is usually present in low-grade areas, the expression of cytokeratin in our case did not agree with this diagnosis. The distinctive features of the histological pattern in myxoid liposarcoma were missing. A diagnosis of synovial sarcoma in our patient could not be definite, as she was relatively old and bcl-2 was not expressed. The immunoprofile of the tumor cells did not fit a diagnosis of low-grade fibromyxoid sarcoma. Thus, our case cannot be further categorized into these known differential diagnoses of myxoid spindle cell sarcoma.

Hallmarked cytogenetic aberrations may have a further diagnostic value in certain spindle cell tumors. The *t* (12;16) (q13;p11) translocation is present in more than 90% of myxoid liposarcomas [13]. The translocation results in the fusion of the DDIT3 gene on chromosome 12 and the FUS gene on chromosome 16. This aberration is highly sensitive and specific for myxoid liposarcoma [14]. In most cases of synovial sarcoma, the *t* (X;18) (p11.2;q11.2)

translocation is present, and results from a fusion gene of SYT on chromosome 18 and SSX1 or SSX2 on chromosome X [15]. The highly specific translocation for synovial sarcoma has also been reported in fibrosarcoma and malignant fibrous histiocytoma [16]. A wide variety of aberrations have been detected in patients with myxoid fibrosarcoma [17]. No specific translocation has been determined. The reports of cytogenetic aberrations are limited and inconclusive in low-grade fibromyxoid sarcoma.

Owing to the scarcity and variety of myxoid spindle cell sarcomas, the understanding of responses to treatment is limited and the outcomes are diverse. Current understanding of the various treatment modalities mostly comes from larger series of soft tissue sarcoma where the sarcoma involving the chest or the pleura is absent or less obtrusive. Radical surgical resection is the only curative procedure in appropriate clinical situations [6-7, 9]. Adjuvant radiotherapy is usually suggested for patients with resectable high-grade sarcomas, and the benefits of adjuvant chemotherapy are controversial and undetermined [18]. In some cases, surgery may bring unacceptable morbidities, or a radical resection is not possible. Definitive radiotherapy may be considered in such situations [19]. The tumor size may affect the rate of local control, but not outcomes. The favorable prognostic factors in definite radiotherapy are an early stage of sarcoma and a larger total dose of radiation [19]. Our patient responded poorly to radiotherapy, which may be attributed to the extensive involvement and the advanced stage.

Spindle cell sarcomas of the pleura are rare. Different subtypes share a great similarity and pose difficulties in diagnosis. Clinical and histological features are always crucial. Immunohistochemical studies are often needed to draw a conclusion; cytogenetic studies may provide more insightful information. Surgery is the treatment of choice in patients with resectable sarcomas. The therapeutic effects of adjuvant therapies remain uncertain. Definitive radiotherapy may play a role in inoperable situations.

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高惡性度之肋膜黏液性紡錘細胞肉瘤

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紡錘細胞肉瘤為罕見的軟組織腫瘤，由原始間質細胞產生，並有廣泛而多樣的組織細胞分形。這些肉瘤有著多元的表現與分岐的預後。在紡錘細胞肉瘤中，有一群腫瘤其紡錘細胞包埋在含有豐富黏液性的基質體中，為黏液性紡錘細胞肉瘤，大多發生在周邊四肢，而罕見原發於肋膜。要區分黏液性紡錘細胞肉瘤不同之亞型有相當之困難度。我們在此提出一個以大量肋膜積水表現的原發性肋膜高惡性度黏液性紡錘細胞肉瘤的個案。胸腔鏡下觀察發現在肋膜腔內有大量凝膠狀、肉瘤狀的無定形腫瘤。病理檢查確立為高惡性度黏液性紡錘細胞肉瘤。手術移除只能提供暫時性的緩解，放射線治療並無法遏止腫瘤在手術後的迅速惡化。綜合臨床表現與病理檢查的結果，此肉瘤與目前文獻已報告的亞型均有差異之處。為一獨特的表現。黏液性紡錘細胞肉瘤並不易診斷或分類，我們藉這個特殊的病例將可能鑑別診斷之亞型間的臨床病程、組織型態、免疫染色、預後與治療作一綜論與分析。*(胸腔醫學 **2009; 24: 60-67**)*

關鍵詞：黏液性紡錘細胞肉瘤，肋膜腫瘤

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Malpositioned Central Venous Catheter in the Main Pulmonary Artery Trunk – A Case Report

Jui-Yuan Lin, Ping-Hung Kuo, Jin-Shing Chen*

Central venous catheterization may provide hemodynamic information and act as a route for the rapid infusion of fluids and therapeutic agents. The complications of central venous cannulation are numerous. Vascular injuries during central venous catheter (CVC) insertion encompass a wide spectrum of complications, with arterial puncture being the most common. We report a 67-year-old woman with profound septic shock in whom the main pulmonary artery trunk was accidentally cannulated during an attempt to establish central venous access. Mini-thoracotomy for CVC removal was performed. Minimal pneumothorax and some reddish pleural effusion were found. The postoperative hemodynamic status was stable. We also reviewed the related literature on complications and pulmonary artery injury during central venous catheterization. ***(Thorac Med 2009; 24: 68-73)***

Key words: central venous catheter, malposition, pulmonary artery

Introduction

Central venous catheterization may provide hemodynamic information and act as a route for the rapid infusion of fluids and therapeutic agents. The complications of central venous cannulation are numerous and include malpositioning, arterial puncture, pneumothorax, hemothorax, chylothorax, mediastinal hematoma, injury to adjacent nerves, extravasation of the infusate, thrombophlebitis, and infection [1-2].

Malpositioning is a well-recognised complication of central venous cannulation, occurring in up to 1.8% of cases, depending on the insertion site and the experience of the operator [3]. Vascular injuries during central venous catheter (CVC) insertion encompass a wide spectrum of complications, with arterial puncture being the most common [4]. Malpositioning occurs more frequently with internal jugular venous and femoral venous access than with subclavian venous access, and even though this complication is usually self-limiting, it should not be dismissed as inconsequential because it can lead to substantial morbidity or death, even if the puncturing needle is of a relatively small gauge or the catheter is correctly placed in its intended venous location [4].

In this case report, we would like to present an adult patient with profound septic shock

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in whom the main pulmonary artery (PA) trunk was accidentally cannulated during an attempt to establish central venous access.

Case Report

A 67-year-old woman was transferred to our hospital because of urosepsis with profound septic shock and sudden collapse with pulseless electrical activity. She underwent cardiopulmonary resuscitation at a local hospital, with return of the sinus rhythm spontaneous circulation. Her past history was notable for diabetic mellitus, hypertension, depression-mania, recurrent urinary tract infection and an old cerebral vascular accident.

On admission, physical examination revealed a Glascow coma scale of E1M1Vt, dilated pupils, tachycardia of 117 bpm, a respiratory rate of 21 breaths/minute, body temperature of 36.5^{o}C, and arterial blood pressure of 99/33 mmHg under dopamine 20 μg/kg/min. An attempt to establish central venous access through the left subclavian vein was unsuccessful and an arterial puncture was noted. During the second trial, the CVC was cannulated and aspiration of venous blood through the catheter occurred.

A portable chest radiograph following the procedure revealed a lung intubation into the right main bronchus and an aberrantly positioned CVC (Figure 1). At our intensive care units, the endotracheal tube was repositioned and another CVC was inserted through the right femoral vein for infusion of fluids and therapeutic agents. Chest-abdomen-pelvis computed tomography (CT) was performed on the third day of admission (Figure 2), and showed that the malpositioned CVC was located from the left anterior first intercostal space to the anterior mediastinum, and directly into the root of the PA, escaping the left brachiocephalic vein. CT also showed mild bilateral pleural effusion and pericardial effusion. Bedside transthoracic echocardiography revealed no pericardial tamponade.

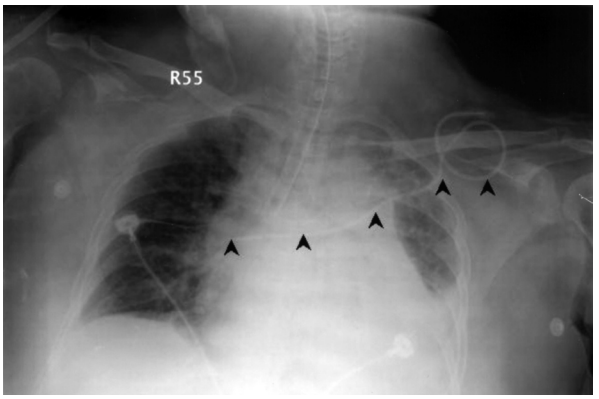
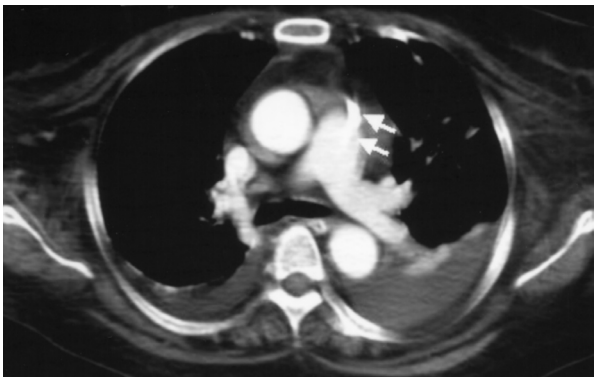
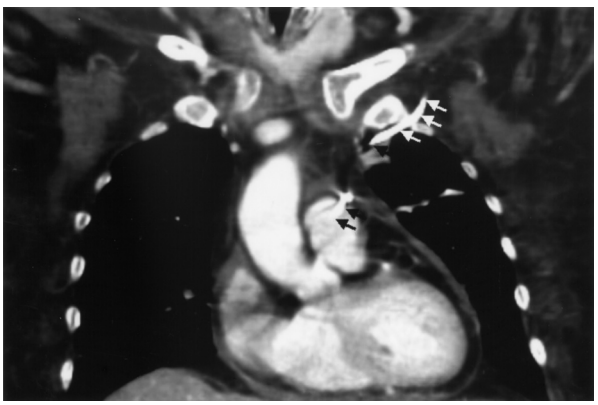


Fig. 1. Chest radiograph showing lung intubation into the right main bronchus, reduction of left lung volume, and an aberrantly positioned central venous catheter (arrowheads).

Inotropic agents were tapered off on the fourth day of admission. Mild wound oozing from the malpositioned catheter was noted and blood component therapy was instituted. A cardiovascular surgeon was consulted for removal of the aberrantly positioned CVC. Mini-thoracotomy for CVC removal was performed on the ninth day of admission (Figure 3). The operation was performed from the left anterior third intercostal space. A camera port was inserted from the mid-axillary line of the left sixth intercostal space. The CVC was found at the main PA trunk, and minimal pneumothorax and some reddish pleural effusion were also found. A purstring suture with 4-0 prolene around the CVC was done. The CVC was removed smoothly and hemostasis was performed. The postoperative hemodynamic status was stable. She was extubated and successfully liberated from mechanical ventilation on the eighteenth day of admission. Then, she was transferred to our



(A)



(B)

Fig. 2. Chest computed tomography (CT) revealing malpositioning of a central venous catheter (arrows) at the main pulmonary artery trunk (Panel A). Reconstruction of chest CT images shows a central venous catheter (arrows) insertion from the left anterior first intercostal space to the anterior mediastinum and directly into the root of the pulmonary artery, escaping the left brachiocephalic vein (Panel B). Mild bilateral pleural effusion and pericardial effusion are also noted.

general ward for further care and management.

Discussion

Injuries to the PA result more commonly from the use of PA catheters [5-7], although occasionally the vessel is punctured directly during CVC insertion attempts [8-9]. The estimated incidence of PA catheter-associated injury—hemorrhage and infarct—is 0.1% to 0.2%,

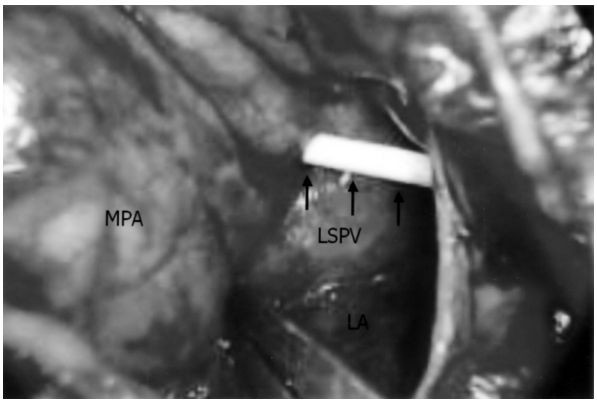


Fig. 3. Mini-thoracotomy showing a central venous catheter (arrows) at the main pulmonary artery trunk. MPA: main pulmonary artery trunk; LSPV: left superior pulmonary vein; LA: left atrium.

with a mortality rate of 42% [5, 7]. Only 2 case reports of PA puncture during CVC insertion attempts were found [8-9], and both cases required emergency thoracotomy.

Hirsch *et al*. reported a case of PA puncture which resulted in cardiac tamponade following insertion of a cannula into the subclavian vein. In their report, 6 hours elapsed before cardiac tamponade became apparent. Median sternotomy and release of the hemopericardium were performed. A needle puncture site at the apex of the PA and a similar hole in the anterior pericardium were seen. Their patient made a complete recovery after the operation [9].

In our case, the CVC was inserted from the left anterior first intercostal space to the anterior mediastinum, bypassing the left brachiocephalic vein and going directly into the main PA trunk. No pericardial tamponade was found. When we consider both of these cases and the anatomy, it is obvious that these complications arose from inserting the introducing needle in an inferior-posterior direction at too great a depth. Another important factor contributing to this iatrogenic complication in our case is that the CVC was not inserted via an infraclavicular approach and

not directly towards the suprasternal notch.

The optimal therapy for hemorrhage control in PA perforation is controversial. Surgical treatment was associated with an increased mortality compared with conservative therapy (43% versus 20%) in previous studies [5]. The clinical and radiologic findings in suspected PA perforation will determine the need for surgical intervention [5]. Operations are recommended in hemodynamically unstable patients with or without airway hemorrhage, in suspected injury to the central branch PAs, and in extensive lobar hemorrhage or intrapleural bleeding [5]. Operations may also be indicated in patients with a suspected PA pseudoaneurysm, with its high propensity for rupture, and if a hemorrhage recurs after embolization of a bleeding perforation [5].

In our case, no significant hemothorax, pneumothorax, pericardial tamponade or hemoptysis was noted after puncture of the PA trunk. A cardiovascular surgeon was consulted immediately after the accident, but surgery was delayed for 1 week because the surgeon thought that the patient's septic shock was still not resolved at that time, and the patient's family also refused immediate surgical intervention.

The incidence of CVC complications is affected by a variety of factors, such as inexperience, the number of needle passes, body mass index >30 or <20 [10-11], previous catheterization, severe dehydration or hypovolemia, and large catheter size [4]. Unsuccessful insertion attempts are the strongest predictor of insertion complications [12]. Complications develop in 28% of patients who fail attempts at catheterization [12].

Common causes of malpositioning of a CVC include the insertion site, clinician's experience, direction of the J-tip of the guidewire [13] and venous stenosis or occlusion [14]. Prior surgery or radiotherapy may cause a slight shifting of the position of the subclavian vein or an alteration of the surface landmarks used to locate the vein [12]. In our case, a lung intubation with subsequent left lung atelectasis and a slight mediastinal shift to the left side might also have contributed to an aberrantly positioned CVC.

Ultrasound guidance may be helpful in central venous catheterization [4]. Successful aspiration of blood, as in the case reported herein, does not exclude the malpositioning of a CVC. Correct positioning of the catheter must be verified using appropriate methods, including chest X-ray, intracardiac ECG tracing, or display of the central venous pressure curve on a monitor [15-16]. Noninvasive bedside tests such as venography with simultaneous chest radiography or transthoracic echocardiography using the agitated saline bubble test can help determine the precise location of a malpositioned CVC [17]. These tests are important diagnostic options when conventional CT of the thorax is not an option [17].

In conclusion, a specific knowledge of anatomy, advanced operating skills, and meticulous attention to detail are key to safe and successful central venous catheterization. A malpositioned CVC can be a diagnostic pitfall on chest radiography. A high index of clinical suspicion and the institution of appropriate therapy are imperative in order to prevent the catastrophic consequences of a malpositioned CVC.

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中心靜脈導管異位置放於主肺動脈幹內——一病例報告

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置放中心靜脈導管可以提供血液動力學的資訊與作為快速輸注液體和治療製劑的管道。有許多種中心靜脈導管置放術的併發症，包括異位、動脈穿刺、氣胸、血胸、乳糜胸、縱隔血腫、鄰近的神經受傷、輸注物外滲出血管、血栓靜脈炎和感染。中心靜脈導管置放過程中造成血管受傷包括多種併發症，其中以動脈穿刺為最常見。我們報告一個67歲女性合併深度的敗血性休克，在試圖建立中心靜脈導管過程中，將導管意外地放置在主肺動脈幹內。中心靜脈導管藉由實行微型胸廓切開術而移除。極少量氣胸與些許紅色肋膜積液被發現。術後的血液動力學狀況穩定。我們回顧了有關中心靜脈導管置放過程中造成的併發症與肺動脈受傷相關之文獻報告。*(胸腔醫學* ***2009; 24: 68-73)***

關鍵詞：中心靜脈導管，異位，肺動脈

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