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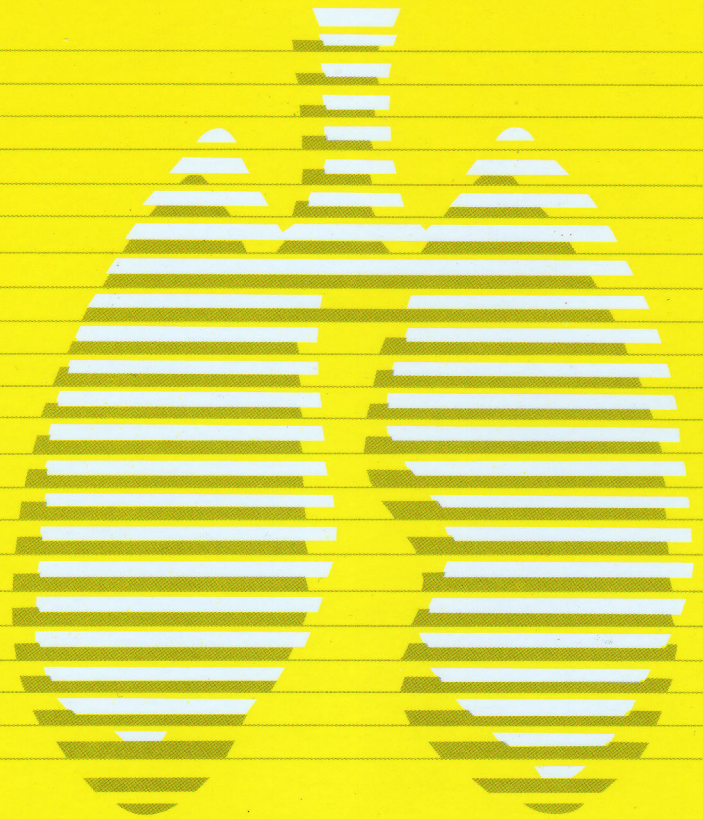

台灣胸腔暨重症加護醫學會

83301 高雄市鳥松區大埤路 123 號

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原著

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Orginial Articles

Case Reports

Long-Term Outcome of Patients that Survived Sepsis after Intensive Care

Henry Hon-Lai Wong*, Chien-Min Chu*, Chung-Chieh Yu*, Yu-Chih Liu*,**, Teng-Jen Yu*, Chung-Ching Hua*, Huang-Pin Wu*,**

Introduction: There have been few studies in Taiwan analyzing the long-term outcome of sepsis patients discharged from the intensive care unit (ICU). Thus, we designed a study to survey the 5-year mortality of ICU patients that survived sepsis.

Methods: Patients whose records were in the database used in our previous prospective study and who were admitted to the Keelung Chang Gung Memorial Hospital medical ICU were followed. Mortality rates of the survivors after ICU discharge and factors that affected long-term mortality were analyzed.

Results: Of the 494 patients admitted to the ICU, 204 survivors were found. Their 5-year mortality rate was 85.3%, and the 1st and 2nd year mortality rates were 60.3% and 71.1%, respectively. Age, past history of diabetes mellitus, malignancy and stroke were positively associated with long-term mortality.

Conclusion: Five years after ICU discharge, the survival rate was only 14.7%. Mortality was positively associated with old age, diabetes, malignancy and stroke history. ***(Thorac Med 2019; 34: 1-10)***

Key words: sepsis, intensive care unit, long-term outcome, critical care

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. It is also a common indication for admission to the medical intensive care unit (ICU) [2]. Despite recent advances in treating critically ill patients, mortality due to sepsis is still high. A study on 2 large hospital cohorts suggested sepsis contributed to 1 of every 2 to 3 hospital deaths [3]. It is known that age, physiologic scores reflecting the severity of the acute illness, the need for invasive or life-supporting procedures, and health status may influence the short-term outcomes of ICU-treated patients [4]. Data on the long-term outcome are essential to appreciate the overall effectiveness of intensive care of critical patients [5]. Factors associated with long-term mortality should also be identified. These factors could help physicians focus more on sepsis patients that have a high risk of long-term mortality.

*Division of Pulmonary, Critical Care, and Sleep Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan; **Chang Gung University, College of Medicine, Taoyuan, Taiwan
Address reprint requests to: Dr. Huang-Pin Wu, Division of Pulmonary, Critical Care and Sleep Medicine, Chang Gung Memorial Hospital, Keelung, #222, Maijin Road, Anle District, Keelung City 20401, Taiwan

In Taiwan, studies that analyze the long-term outcomes of adult ICU patients with sepsis are scarce. Previous studies on the ICU outcome of Taiwanese patients are limited to short-term outcomes and do not include patient details [6]. In this study, we aimed to survey the long-term outcome of patients with sepsis discharged from the ICU and identify factors related to long-term mortality.

Methods

Subjects

This study was a secondary analysis of our previous cohort study [7] and was approved by the Institutional Review Board of Chang Gung Memorial Hospital (98-1682C, 201700223BO). Informed consent was waived. Patients admitted to the medical ICU at Keelung Chang Gung Memorial Hospital for sepsis from July 2007 to June 2010 were recruited for analysis. The following data were recorded within the first 3 days after admission: age, gender, medical history, APACHE II score, and adverse events during admission.

Definitions

Sepsis, according to the Third International Consensus Definitions for Sepsis (Sepsis-3), is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [8]. We defined non-survival as all-cause mortality verified by hospital records and phone verification by family members. Survivors were defined as patients who were still alive 5 years after discharge from the ICU, which was confirmed by hospital records and phone verification by the patients.

Statistical analysis

Statistical analysis was performed using SPSS version 22 statistical software. Continuous variables between the 2 groups were compared using Student's *t* test. Categorical variables were analyzed with the Chi square test or Fisher's exact test. Cox regression analysis was performed to identify predictors of long-term mortality. Standard Kaplan-Meier and log-rank tests were used for survival analysis. A *p*-value less than 0.05 was considered to be statistically significant.

Results

In all, 494 patients were admitted to the medical ICU between April 2007 and July 2010 (Figure 1); 112 patients were excluded for repeated admissions, loss to follow-up or missing mortality records; 178 patients died during the ICU stay. The 204 patients that were discharged alive were enrolled into this study.

The clinical characteristics of the 204 patients that survived their ICU stay are listed in Table 1. The survivors were significantly younger than the non-survivors. The mean APACHE II scores were 22.1 and 24.7 for the survivors and non-survivors, respectively. The patients who did not survive 5 years after discharge were significantly older, had a higher percentage of hypertension and a history of stroke. Of note, the non-survivors had a lower percentage of bacteremia during their ICU stay than those who survived. There was no significant difference in pathogens between survivors and non-survivors 5 years after ICU discharge (Table 2).

The overall 1- and 2-year mortality rates after ICU discharge were 60.3% and 71.1%, respectively. Five years after ICU discharge,

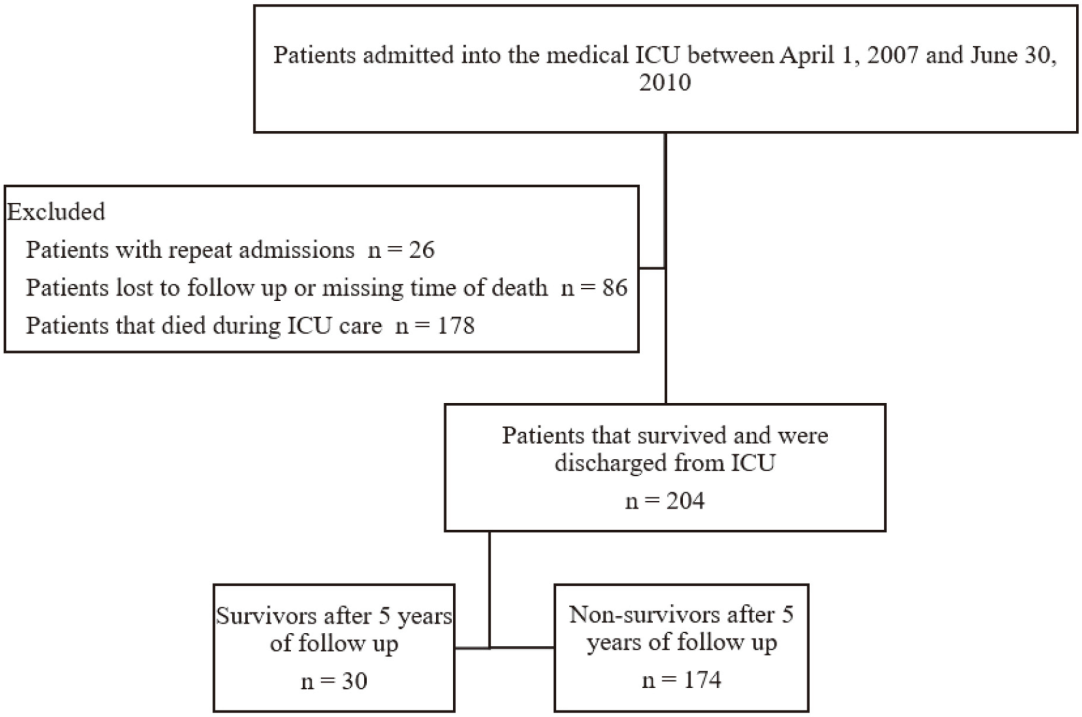

Fig. 1. Flow chart of patients admitted into our medical intensive care unit

14.7% of the 204 patients remained alive (Figure 2). Multivariate Cox regression analysis (Table 3) revealed that age, bacteremia, medical history of stroke, malignancy, heart failure and diabetes mellitus were significant independent factors associated with mortality after ICU discharge. History of hypertension was not an independent factor of long-term mortality of those who were discharged alive from the ICU.

Discussion

Our findings are important because each patient admitted to the ICU in our study had a specific medical history available and we could use that information to identify factors related to long-term mortality. No other available studies that have reported on survival rates of ICU populations in different institutions in Taiwan have included a long-term follow-up.

Our data show that over half of the patients did not survive the first 2 years, and the 5-year mortality rate was 90.2%, which is comparable to other cohorts. Cuthbertson and colleagues reported mortality rates of 54.8% in first 3.5 years and 61% at 5 years [9], whereas Nesseler and colleagues found a 6-month mortality of 45% among patients with septic shock [10]. There is an excess mortality in the population affected by sepsis compared to the general population [11]. And, compared to those without sepsis, survivors of sepsis typically remain at greater risk of post-discharge mortality [12-13] and tend to use more healthcare resources [14].

Despite the fact that ICU patients with sepsis have higher long-term mortality rates than the general population, no definite studies have delved into the reason for this trend. There may

Table 1. Clinical Characteristics of Survivors and Non-Survivors 5 Years after Discharge from the ICU (Number, Percentage; mean±standard Deviation)

	Survivors (n=30)	Non-survivors (n=174)
Gender		
Male	20	110
Female	10	64
Age	60.7 ± 19.5	74.7 ± 12.6*
APACHE score	22.1 ± 9.2	24.7 ± 6.7
Medical history		
Arrhythmia	3 (10.0)	16 (9.2)
Malignancy	2 (6.7)	37 (21.3)
Chronic pulmonary disease	2 (6.7)	32 (18.3)
Heart failure	4 (13.3)	17 (9.8)
Hypertension	10 (33.3)	97 (55.7)*
Cirrhosis	1 (3.3)	16 (3.4)
End-stage renal disease	3 (15)	18 (10.3)
Diabetes mellitus	9 (30)	63 (36.8)
Stroke	2 (6.6)	62 (35.6)*
Co-morbidities		
Thrombocytopenia	11 (36.7)	43 (24.7)
Bacteremia	8 (26.7)	12 (6.9)*
Jaundice	3 (10.0)	10 (5.7)
Shock	12 (40.0)	55 (31.6)
Acute kidney injury	10 (33.3)	61 (35.1)
Gastrointestinal bleeding	4 (13.3)	19 (10.9)
Acute myocardial infarction	0 (0.0)	1 (0.6)
Nature of infection		
Pneumonia	25 (83.3)	134 (77)
UTI	3 (10)	22 (12.6)
Others	2 (6.6)	18 (10.3)
Acute respiratory failure	25 (83.3)	153 (87.9)
Renal replacement therapy	6 (20)	26 (14.9)
Use of low-dose steroid	13 (43.3)	61 (35.1)

* $p<0.05$ compared with survivor group by T test, Chi-square test, or Fisher's exact test

ICU=intensive care unit, APACHE=acute physiology and chronic health evaluation, UTI=urinary tract infection.

be a variety of mechanisms that contribute to the increased long-term mortality after infection and sepsis. Yende *et al*. speculated that sepsis may induce upregulation of pro-inflammatory markers after infection, which may persist after discharge and contribute to the long-term outcomes [15]. However, an immunosuppressive state caused by a prolonged anti-inflammatory

Table 2. Pathogens of Survivors and Non-Survivors 5 Years after ICU Discharge (Number, Percentage of Total)

Pathogens	Survivors (n=30)	Non-survivors (n=174)	Total
Staphylococcus aureus	5 (16.7)	30 (17.2)	35 (17.2)
Acinetobacter baumannii	3 (10)	19 (10.9)	22 (10.8)
Pseudomonas aeruginosa	3 (10)	33 (19)	36 (17.6)
Klebsiella pneumoniae	2 (6.7)	25 (14.4)	27 (13.2)
Escherichia coli	1 (3.3)	23 (13.2)	24 (11.8)
Enterobacter	1 (3.3)	3 (1.7)	4 (2.0)
Candida	0	5 (2.9)	5 (2.5)
Citrobacter	0	3 (1.7)	3 (1.5)
Streptococcus pneumonia	0	4 (2.3)	4 (2.0)
Stenotrophomonas maltophilia	1 (3.3)	4 (2.3)	5 (2.5)

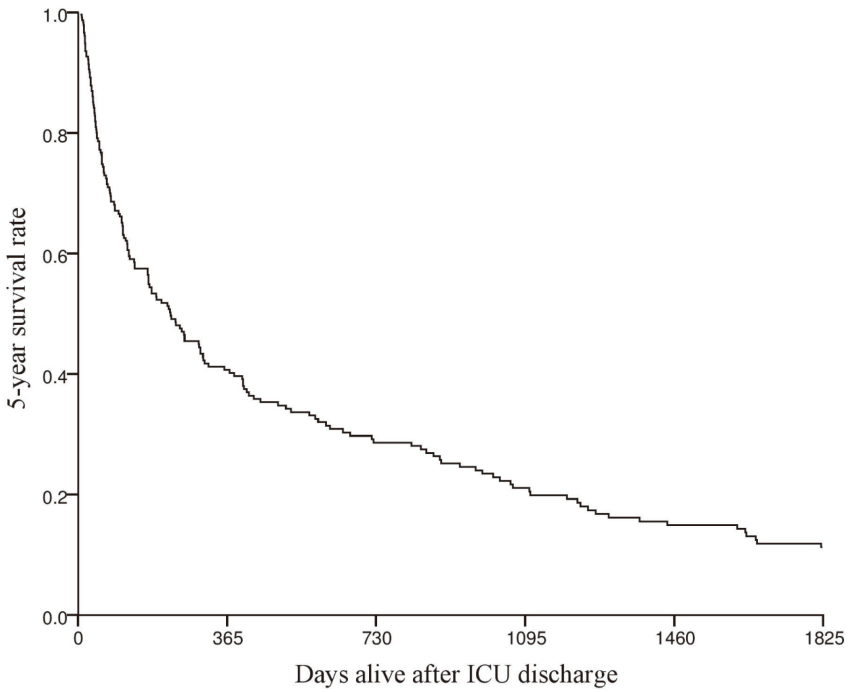

Fig. 2. Kaplan-Meier curve for all 204 patients discharged alive from the ICU after intensive care treatment

response during sepsis was recently suggested possibly to affect long-term outcomes in septic patients [16]. An alternative explanation is that patients hospitalized with sepsis may differ from the background population with respect to the presence of different comorbidities, which also could affect their long-term outcome. However, in our study, the presence of comorbidities such as chronic obstructive pulmonary disease, heart failure, cirrhosis, end stage renal disease or type 2 diabetes did not affect the long-term outcomes of sepsis patients discharged from the

Table 3. Multivariate Cox Regression Analysis to Determine Independent Factors of Patient Mortality

Variables	HR	95% CI	*P* value
Sex	0.941	0.699-1.322	0.724
Age	1.022	1.008-1.037	0.002
APACHE II Score	1.018	0.993-1.043	0.157
Medical history			
COPD	1.273	0.817-1.983	0.286
Arrhythmia			
Malignancy	1.799	1.177-2.750	0.007
Heart failure	0.510	0.291-0.893	0.018
Hypertension	1.282	0.919-1.787	0.143
Liver cirrhosis	1.084	0.580-2.025	0.801
ESRD	1.150	0.547-2.241	0.712
Diabetes mellitus	1.547	1.058-2.262	0.024
Stroke	1.707	1.182-2.465	0.004
Co-morbidities			
Thrombocytopenia	1.097	0.739-1.631	0.645
Bacteremia	0.436	0.225-0.845	0.014
Jaundice	1.080	0.501-2.328	0.845
Shock	1.685	0.953-2.978	0.073
Acute renal failure	1.108	0.760-1.615	0.595
AMI	2.345	0.281-19.555	0.431
Nature of infection			
Pneumonia	1.337	0.785-2.278	0.285
UTI	1.569	0.882-2.790	0.125
Others, as reference			
Acute respiratory failure	1.550	0.910-2.640	0.107
Renal replacement therapy	0.675	0.363-1.255	0.215
Use of low-dose steroid	0.654	0.383-1.116	0.120

HR=hazard ratio; CI=confidence interval; APACHE=Acute Physiology and Chronic Health Evaluation; COPD=chronic obstructive pulmonary disease; ESRD=end-stage renal disease; AMI=Acute myocardial infarction

ICU.

Univariate analysis revealed that advanced age contributed to higher long-term mortality rates among our ICU patients with sepsis after discharge, which is consistent with other studies. Lemay *et al* reported increasing age is associated with long-term mortality rates among elderly patients with sepsis [17]. We also found that diabetes was an independent predictor of early death among patients with sepsis after discharge from the ICU. This association between diabetes and long-term mortality after sepsis was expected, given the reportedly high risk of hospitalization from infection such as pneu-

monia in diabetic patients, and the high risk of complications from infectious illness among these individuals [18-20]. Patients with malignancy may also have an increased risk of severe infections leading to sepsis. Several studies have reported poor outcomes for sepsis patients with malignancy [21-22]. Our data further confirm the higher long-term mortality rates among sepsis patients with malignancy.

The presence of heart failure in this study was associated with a decreased risk of death in critically ill patients discharged from the ICU. However, since most patients with heart failure are admitted into the cardiac care unit, not the medical ICU, in our hospital, this finding could be attributed to the limited number of patients with heart failure in this study. We also observed an association between bacteremia and a decreased risk of long-term mortality in our cohorts; this finding is in contrast to that of a large study showing that bacteremia had a negative impact on long-term mortality [23]. Further study is needed to confirm the association between heart failure, bacteremia and long-term mortality in sepsis survivors after ICU discharge.

We found that patients with a medical history of stroke who were admitted to the ICU due to sepsis had higher long-term mortality than those without a stroke history. This finding may reflect the vulnerability of stroke patients to long-term post-stroke complications, leading to a poorer prognosis when they are affected by sepsis. According to a retrospective cohort study by Bravata *et al*., patients who were discharged alive after being hospitalized due to acute ischemic stroke were readmitted at least once during a 5-year follow-up; 53% of the patients were hospitalized again during the first year after hospital discharge, and the most common diagnoses were respiratory illnesses and pneumonia [24]. Furthermore, a study by Berger *et al*. found that the presence of sepsis in stroke patients admitted to the neurology ICU was associated with a worse outcome at discharge and after 3 months, compared to the control group [25]. Medical complications such as pneumonia and sepsis that occur after acute ischemic stroke interfere with subsequent functional recovery, and this can be associated with severe medical events [26].

The limitations of our study include the considerable number of patients we were not able to contact after discharge due to either a change of address or a lack of contact information, which may affect the outcome of our study. In addition, due to the lack of official mortality data, we were unable to examine the exact causes of death to further evaluate the impact of ICU admission due to sepsis on long-term mortality. Finally, our dataset did not contain the data needed to make use of the Charlson Comorbidity Index, a tool that predicts outcomes in different clinical populations [27], which could strengthen our results to predict and estimate the risk of death from comorbid disease among sepsis patients after ICU discharge.

Conclusion

Our study found high 5-year mortality rates among survivors of sepsis after discharge from our medical ICU. These high mortality rates were associated with age and history of stroke, malignancy and diabetes mellitus. A more complete local or national registry of ICU admissions should be created so that more thorough studies can be performed to develop specific strategies that guide clinicians in the manage-

ment of post-critical care patients.

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敗血症患者重症照護後的長期預後

黃翰禮 * 朱建民 * 于鍾傑 * 劉育志 *,** 游騰仁 * 花仲涇 * 吳黃平 *,**

前言：目前很少有研究分析台灣敗血症重症患者的長期預後。因此我們設計了一項研究來探討敗血症倖存者的 5 年死亡率。

方法：我們追蹤之前所使用的前瞻性研究數據庫中入住基隆長庚醫院內科加護病房的病患。分析 ICU 出院後病患的死亡率，並確定影響長期死亡率的因素。

結果：在連續三年內接受內科加護病房治療的 494 例患者中，共發現 204 例加護病房存活患者。他們的 5 年死亡率為 85.3%，而第一年和第二年的死亡率分別為 60.3% 和 71.1%。年齡，糖尿病、癌症和中風病史與長期死亡正相關。

結論：ICU 出院 5 年後存活率僅為 14.7%。我們發現五年死亡率和年齡，糖尿病、癌症和中風病史有正相關的現象。*(胸腔醫學 **2019; 34: 1-10**)*

關鍵詞：敗血症，加護病房，長期預後，重症

* 基隆長庚紀念醫院　胸腔暨重症加護及睡眠醫學科，** 台灣桃園長庚大學醫學院
索取抽印本請聯絡：吳黃平醫師，基隆長庚紀念醫院　胸腔暨重症加護及睡眠醫學科，基隆市安樂區基金一路 208 巷 200 號

Disseminated Tuberculosis with Multiple Skeletal Involvement Mimicking Multiple Bone Metastases: A Case Report

Chia-Jung Liu, Jann-Yuan Wang

Musculoskeletal tuberculosis (TB) is the third most common type of extra-pulmonary TB, following pleural and lymphatic involvement, in the United States. Although not uncommon, early diagnosis of skeletal TB remains a challenge, probably due to its indolent course and nonspecific clinical manifestations. Here, we reported a patient with disseminated TB with multiple skeletal involvement who was initially diagnosed as having lung cancer with multiple bone metastasis. This case reminds us that TB must be considered in the differential diagnosis of multiple skeletal lesions, especially in areas of high TB prevalence. Maintaining a high index of clinical suspicion and collecting specimens for histology examination and mycobacterial culture are crucial to avoid a delayed diagnosis and treatment. ***(Thorac Med 2019; 34: 11-19)***

Key words: bone scan, magnetic resonance imaging, metastasis, multiple bone lesions, skeletal tuberculosis

Introduction

According to an estimate by the World Health Organization (WHO), about one-third of the world's population is infected by *Mycobacterium tuberculosis*, and tuberculosis (TB) is the leading infectious cause of adult death [1]. Musculoskeletal TB, which accounts for about 10% of all extra-pulmonary TB cases, is the third most common type of extra-pulmonary TB, following pleural and lymphatic involvement, in the United States [2].

Although skeletal TB is not rare, making an accurate and timely diagnosis remains a challenge in clinical practice. The onset and progression of skeletal TB are usually slow and insidious. Concomitant pulmonary involvement may present in only 50% of cases [2]. Furthermore, TB has a reputation as a great mimicker in clinical presentation and the diagnosis is often confused with malignancy [1]. As a result of these unfavorable factors, delayed diagnosis of skeletal TB occurs frequently, with a median duration of 4 months between symptoms onset and the correct final diagnosis [3], resulting in increased frequency and severity of complications, such as joint deformity and functional loss [4]. Therefore, getting familiar with skele-

Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Jann-Yuan Wang, Department of Internal Medicine, National Taiwan University Hospital, #7, Chung-Shan South Rd., Zhongzheng Dist., Taipei 10002, Taiwan

tal TB is important for clinicians, so as to avoid an unnecessary delay in, or a missed diagnosis. Here, we report a case of disseminated TB with multifocal skeletal involvement, mimicking malignancy with multiple bone metastases. Differentiating tuberculous and malignant bone lesions is also discussed.

Case Report

This 55-year-old man worked in China; he had an underlying hepatitis B virus infection and was a carrier without regular follow-up. He complained of chronic cough and progressive exertional dyspnea for 5 months. Unintentional weight loss of around 12 kilograms within 2 months was also noted. At first, he was admitted to a local teaching hospital with the tentative diagnosis of community-acquired pneumonia. Serial examinations for an infectious etiology revealed no definite pathogen. After empiric use of moxifloxacin for 7 days, his symptoms improved and he was discharged. However, the respiratory symptoms recurred and aggravated during the following month. Occasional fever up to 38°C was also noted.

On arrival to our emergency department, his blood pressure was 152/105 mmHg, pulse rate 95/min, respiratory rate 20/min, and body temperature 36.7°C. Results of blood tests were as follow: hemoglobin: 12.1 g/dL, leukocyte count: 17.24 K/μL with 76.3% being segmented neutrophils, creatinine: 1.1 mg/dL, C-reactive protein: 15.64 mg/dL (normal value <0.8), calcium: 2.74 mmol/L (normal value 2.15-2.58), and albumin: 3.1 g/dL (normal value 3.5-5). Chest radiography (CR) showed bilateral lung opacities, a widening mediastinum and blunt bilateral costophrenic angles (Supplementary figure). Chest computed tomography (CT) revealed an infiltrative mass in the medial portion of the left upper lung, multiple bilateral varied-size nodules with bilateral pleural effusion, multiple lymphadenopathy with central necrosis in the right supraclavicular area and mediastinum, and destructive lesions in the bilateral ribs and spine (Figure 1). Magnetic resonance imaging (MRI) of the lumbar spine (Figure 2) revealed multifocal small fluid-like nodular lesions with rim gadolinium enhancement at the L3-L5 spine. He was hospitalized with the tentative diagnosis of lung cancer with lung and bone metastasis complicated with hypercalcemia.

After admission, tumor staging workup was arranged. Brain MRI showed no detectable lesion. Whole body bone scan (Figure 3) revealed active lesions at the right frontal skull, bilateral ribs, pelvic bones and L3 spine, highly suspected to be multiple bone metastases. Bronchoscopy (Figure 4) revealed erythematous mucosa swelling covered by cheese-like material and many rice-like nodules at the bilateral bronchial trees, along with a deep ulcer at the left main bronchus. Histological examination of the endobronchial biopsy of the ulcer and rice-like nodules disclosed focal granulomatous inflammation (Figure 5A). The bronchial washing sample was smear-positive for acid-fast bacilli (AFB) and test-positive for *M. tuberculosis* complex by nucleic acid amplification. Combined anti-TB treatment (isoniazid, rifampin, ethambutol, plus pyrazinamide) was immediately initiated. The bronchial washing sample was culture-positive for *M. tuberculosis* complex.

Given that multiple well-defined bony lesions are an uncommon presentation of TB [2], CT-guided biopsy of the iliac bone and surgical resection of the right 7th rib were performed. Histological reports for both samples indicated

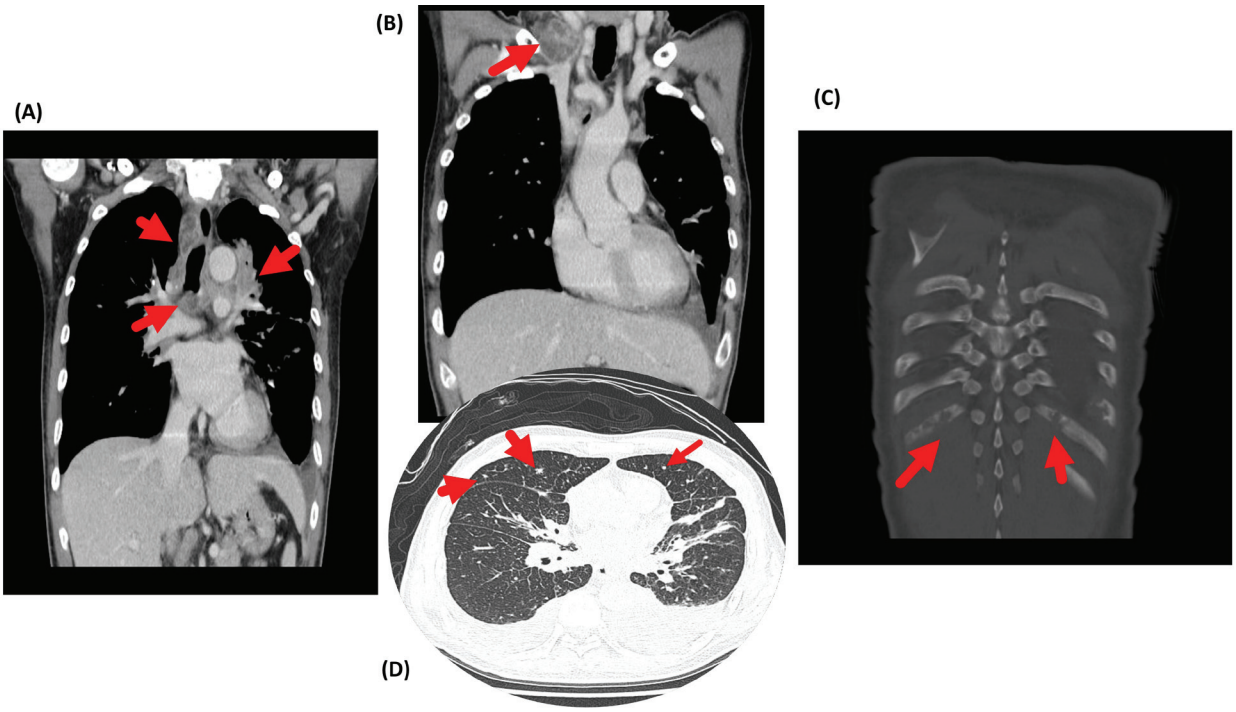


Fig. 1. Chest computed tomography with contrast shows (A) infiltrative mass in the medial portion of the left upper lung and multiple necrotic mediastinal lymphadenopathies, (B) right supraclavicular lymphadenopathy, (C) destructive lesions at the bilateral ribs, and (D) multiple nodules of varied sizes in both lungs and bilateral pleural effusion.

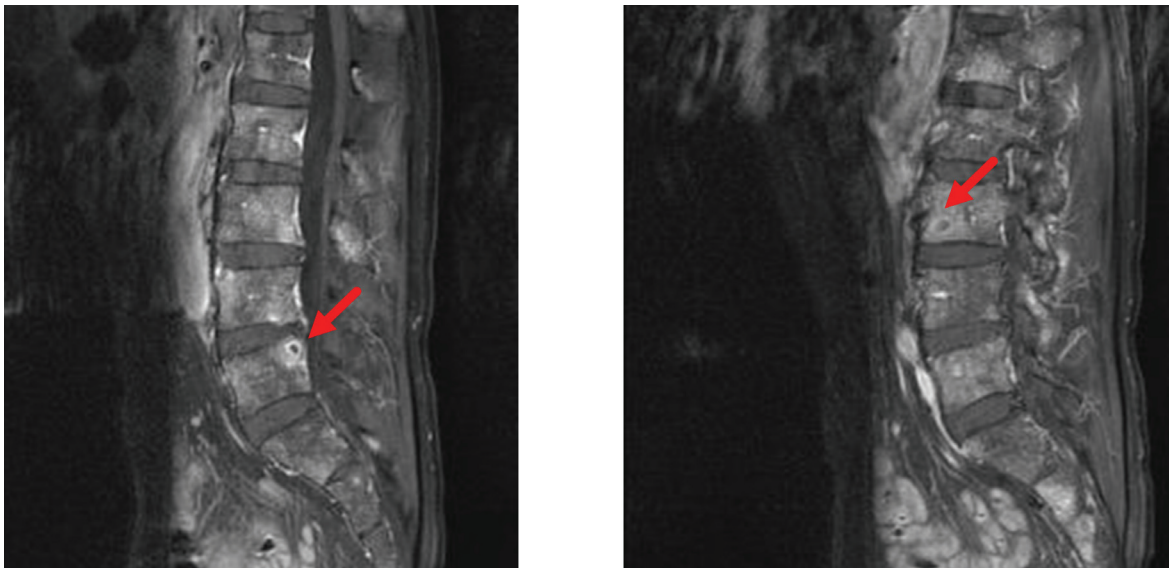


Fig. 2. Magnetic resonance imaging of the lumbar spine with T1-weighted contrast imaging reveals multifocal small fluid-like nodular lesions with rim gadolinium enhancement at the L3 and L5 spine.

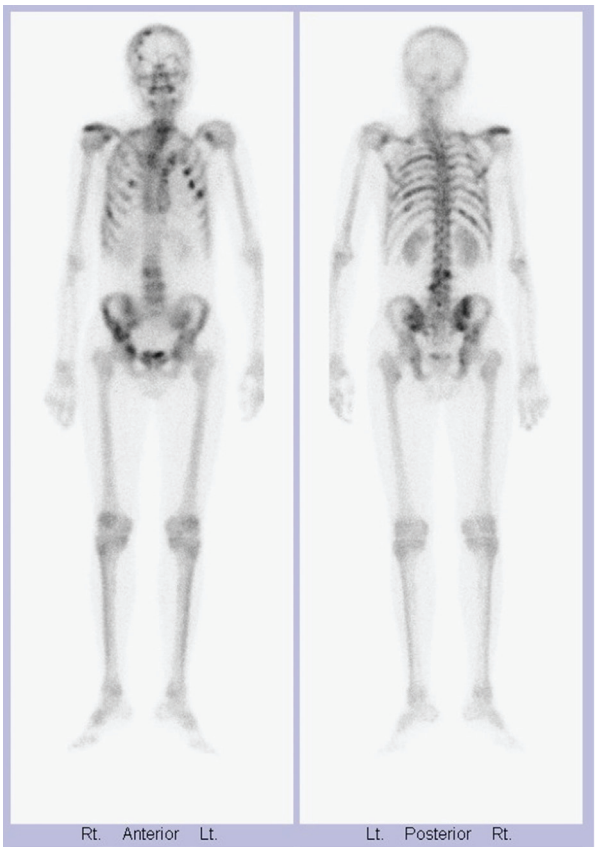


Fig. 3. Whole body bone scan shows multiple lesions with intensive radioactive accumulation at the right frontal skull, bilateral ribs, pelvic bones and L3 spine.

granulomatous inflammation without evidence of malignancy (Figure 5B). The patient was discharged under anti-TB treatment. Follow-up chest CT 6 months later revealed much improvement of the lung and bony lesions (Figure 6). Thus, disseminated TB with multiple bone involvement was finally diagnosed. The drug susceptibility test revealed that the *M. tuberculosis* isolate was susceptible to all 1st-line anti-TB drugs, including isoniazid, rifampin, ethambutol and streptomycin. He completed a 9-month anti-TB treatment course uneventfully.

Discussion

This case report highlights three key learning points. First, TB is a great imitator, being able to masquerade as bacterial pneumonia or malignancy. It should always be considered in patients with chronic illness and multi-organ involvement. Second, multifocal bone lesions found on bone scan do not always imply malignancy. TB should be one of the differential

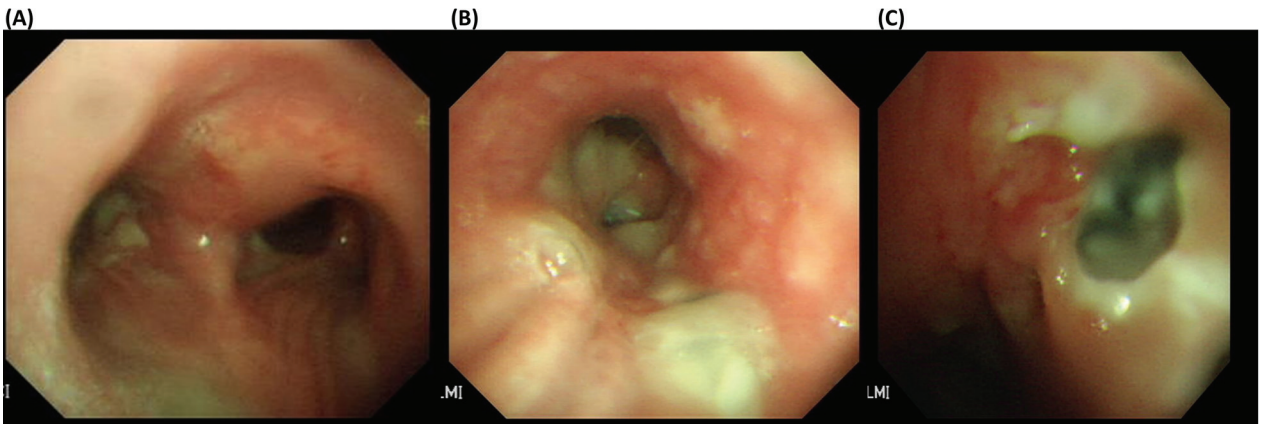


Fig. 4. Bronchoscopy reveals (A) erythematous mucosa swelling covered by cheese-like material, (B) rice-like nodules, and (C) a deep ulcer at the left main bronchus.

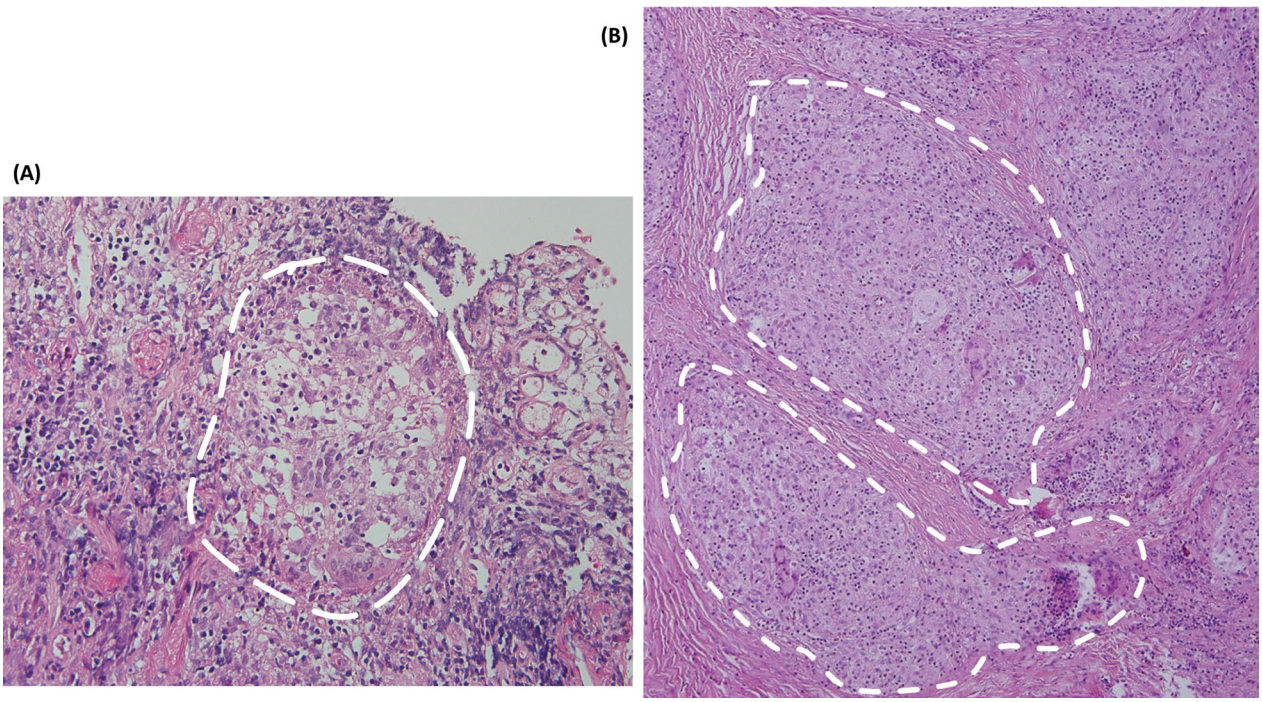


Fig. 5. Histological examination shows (A) focal histiocytic aggregation forming vague granuloma in the bronchoscopic biopsy sample of the left main bronchus ulcer and (B) granulomatous inflammation in the surgical biopsy sample of the right 7th rib.

diagnoses. Third, prompt tissue sampling for histology examination and bacteriology study is essential for rapid diagnosis of skeletal TB.

Vertebrae are the most common site of involvement in skeletal TB, accounting for about half of all musculoskeletal TB cases [5]. Back pain and local tenderness are the most common presenting symptoms, followed by kyphotic deformities and neurological deficits, such as numbness, weakness or even paralysis [2]. Spine MRI is the preferred choice of imaging modality for TB spondylitis because it can detect early marrow and paraspinal soft tissue change [6-7]. The typical radiographic characteristics of TB spondylitis include the following [2]: 1. The anterior component of the vertebral body is much more commonly affected, with sparing of the posterior component; 2. Multiple vertebral involvement, possibly due to contiguous spread along the anterior longitudinal ligaments; 3. Relative sparing of the intervertebral disk; 4. Heterogeneous lesions with a rim enhancement pattern; and 5. Paravertebral abscesses. These findings may serve as clues to differentiate TB spondylitis from a pyogenic or neoplastic etiology. For example, pyogenic spondylitis often destroys the intervertebral disk rapidly, resulting in disk space narrowing at an early stage. The neoplastic process, however, usually does not have paravertebral abscesses [8].

In addition to the vertebrae, the hip and knee are also frequent sites of TB involvement, accounting for 16% and 18% of all skeletal TB cases, respectively [5]. By contrast, rib and skull involvement, as in this case, is a less common manifestation [9]. The latter usually occurs in children or patients with a history of head

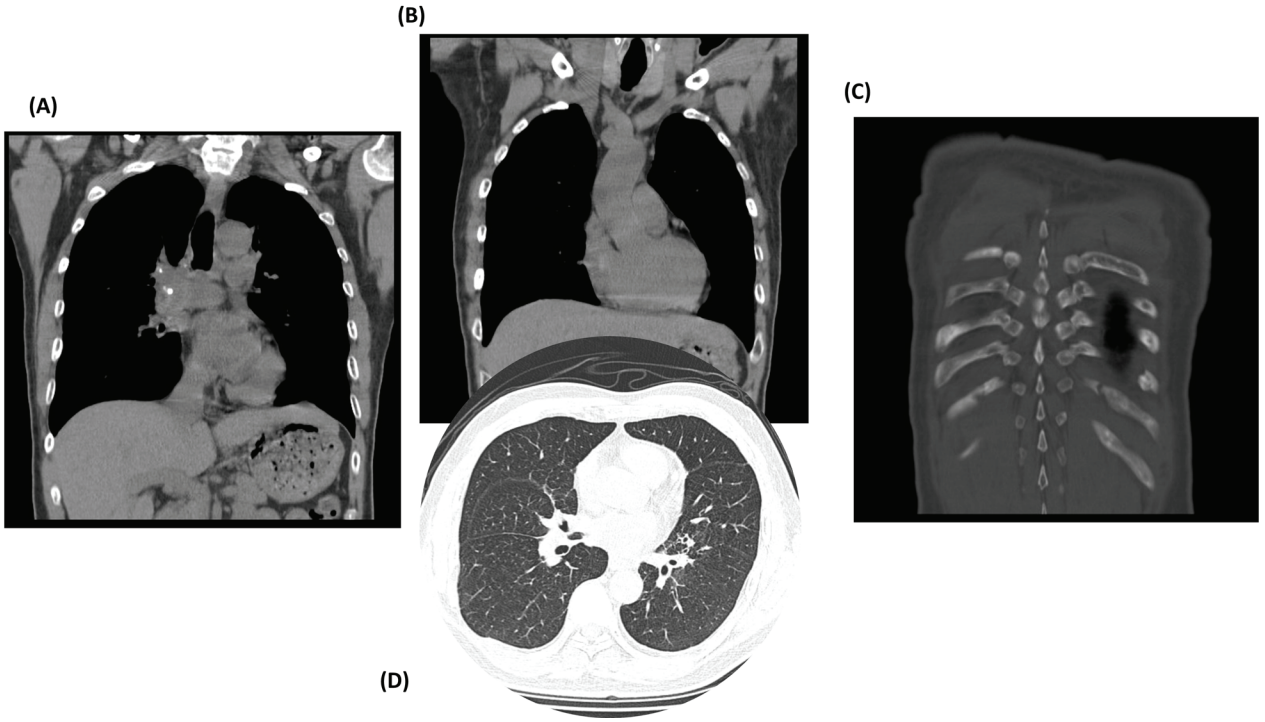
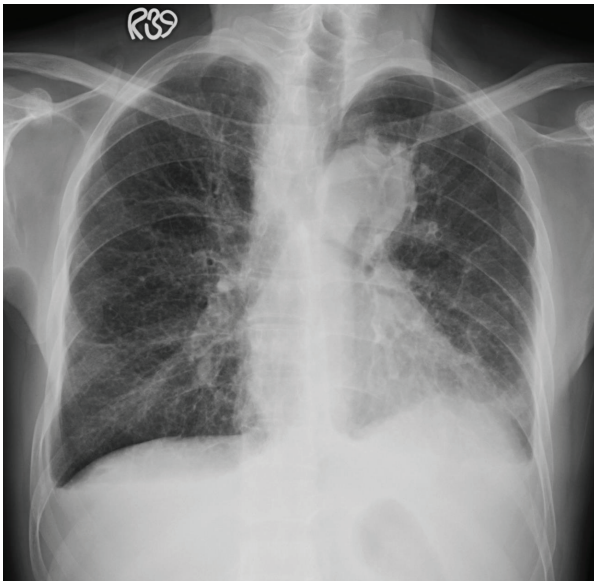


Fig. 6. Follow-up chest computed tomography 6 months later discloses much improvement of the previous lesions in the lung, lymph nodes and bone.

trauma [10], and is probably due to increased vascularity, decreased resistance or unmasked latent infection [10-11]. As for rib TB, the pathogenesis may be hematogenous seeding or contiguous spread via pulmonary TB [2]. Although uncommon, TB is still the second most common etiology of non-traumatic rib lesions, ranking behind malignancy only [12]. Besides, one study conducted in South Africa showed that rib TB is becoming more and more common, while the incidence of spinal TB is decreasing [13].

Whole body bone scan with technetium-99m methylene diphosphonate (Tc-99m MDP) is commonly used to evaluate bone metastasis. This type of scan has the strength to detect any bone remodeling process. The relatively low specificity, however, limits its ability to differentiate malignancy from a benign process such



Supplementary fig. Chest radiography showed bilateral lung opacities, widening mediastinum and blunt bilateral costophrenic angles.

as TB, fibrous dysplasia or enchondroma [14], especially in areas with a high TB prevalence. Thus, prompt tissue sampling with histology examination and bacteriology study is pivotal to make an accurate diagnosis of skeletal TB.

Early initiation of anti-TB treatment for skeletal TB is crucial to prevent subsequent deformity and loss of function. Rifampin-based regimens that are effective for drug-susceptible pulmonary TB are also appropriate for drug-susceptible skeletal TB [2]. Several studies have shown that skeletal TB had a good response to rifampin-based regimens of 6-9 months [15-17], but some experts favored the 9-month treatment duration because of the difficulties in assessing therapeutic response [2]. Due to the excellent response to medical therapy, surgical intervention should be reserved only for patients with refractory infection, spine instability, progressive kyphosis, and spinal cord compression with neurological deficit [2].

In conclusion, early diagnosis of skeletal TB remains a challenge in clinical practice. TB should always be considered for patients with chronic illness and multi-organ involvement. Tissue sampling with microbiological and histopathological examinations is necessary to establish the diagnosis. Full restoration of function without deformity can be expected, if treatment is not delayed.

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播散型結核合併多處骨頭侵犯：病例報告

劉家榮　王振源

肌肉骨頭結核是第三常見的肺外結核病，儘管其發生率不低，在臨床上卻常常有延誤診斷的情況發生，推測可能的原因是骨頭結核的臨床進程較緩慢，且患者的臨床症狀通常較不具特異性。一旦延誤診斷就可能會導致病人產生後續嚴重的併發症，因此如何避免延誤診斷是一個很重要的課題。本篇病例報告提出一位播散型結核合併多處骨頭侵犯的病人，一開始也被懷疑是肺癌合併骨轉移，但經過積極的組織取樣，最終確診是骨結核。在這個案例中，可學習到針對多部位的骨頭病灶，骨結核是必須要考慮的一個鑑別診斷；此外，當臨床上懷疑有骨結核時，必須積極的去取得檢體做培養及病理學化驗來得到最終診斷。
*(胸腔醫學 **2019; 34: 11-19**)*

關鍵詞：骨骼掃描，核磁共振，轉移，多部位的骨頭病灶，骨結核

國立台灣大學醫學院附設醫院　內科部　胸腔科
索取抽印本請聯絡：王振源醫師，國立台灣大學醫學院附設醫院　內科部　胸腔內科，台北市中山南路 7 號

Pulmonary Kaposi's Sarcoma in a Myasthenia Gravis Patient Receiving Immunosuppressive Agents: A Case Report

Chun-Fu Chang, Hsu-Ching Huang, Yi-Chen Yeh*, Chao-Hua Chiu

Primary pulmonary Kaposi's sarcoma is an uncommon complication in patients receiving immunosuppressive agents and may be difficult to diagnose. We reported a 62-year-old female patient who had received azathioprine and prednisolone for myasthenia gravis for 10 years and was found to have pulmonary Kaposi's sarcoma without cutaneous involvement. The diagnosis based on the presence of typical flame-shaped lesions on chest computed tomography and a typical histopathological finding, with positive immunohistochemical staining for human herpesvirus 8 on lung biopsy specimens. The patient received 2 cycles of systemic chemotherapy with pegylated liposomal doxorubicin. However, bacteremia and cytomegalovirus viremia developed during chemotherapy. The patient ultimately died from respiratory failure 6 months after the diagnosis of Kaposi's sarcoma. ***(Thorac Med 2019; 34: 20-27)***

Key words: Kaposi's sarcoma, human herpesvirus 8, azathioprine

Introduction

Kaposi's sarcoma (KS) is a serious complication in patients receiving immunosuppressive agents. Lung involvement of KS is an uncommon condition in patients without acquired immune deficiency syndrome (AIDS). While some typical findings, including flame-shaped lesions in chest computed tomography (CT) and purple-to-bright red endobronchial macular lesions on bronchoscopy, strongly suggest pulmonary KS, histopathological examination of the sample obtained from the lesion may not be conclusive. Detection of human herpesvirus 8 (HHV8) from the tissue sample is helpful in confirming the diagnosis. In immunocompromised patients with newly developed pulmonary lesions without evidence of infection, clinicians should consider the possibility of pulmonary KS or other HHV8-associated diseases.

Case Report

A 62-year-old woman was admitted to the orthopedic ward due to low back pain with the diagnosis of compression fracture of multiple

Department of Chest Medicine, *Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Chao-Hua Chiu, Department of Chest Medicine, Taipei Veterans General Hospital, 201 Section 2, Shih-Pai Road, Taipei, Taiwan

vertebral bodies. During the pre-operative survey, a chest roentgenography (CXR) abnormality was noted. There were no respiratory or systemic symptoms, such as fever, cough, dyspnea, chest pain, decreased appetite, or weight loss. Physical examination revealed lower back knocking tenderness and decreased muscle power in the bilateral lower limbs. No remarkable skin lesion could be identified.

The patient had a history of myasthenia gravis (MG) and diabetes mellitus. Her daily medication included azathioprine (150 mg/day), prednisolone (45 mg/day), pyridostigmine, metformin, and glimepiride. She underwent an extended thymectomy for MG 10 years ago and laparoscopic cholecystectomy for chronic cholecystitis 3 months prior to this admission. The last episode of exacerbation of her MG occurred 1 year ago, with the presentation of dysphagia that resolved after plasma exchange. Since the attempts at titration of her azathioprine and prednisolone led to the recurrence of dysphagia, the dosage of both medications has remained unchanged since then. She was a housewife and a non-smoker, with no history of respiratory diseases such as bronchiectasis, pulmonary tuberculosis, asthma, or chronic obstructive pulmonary disease. There was no recent travel history, and she had not been exposed to patients with infectious diseases. She denied alcohol consumption or herb usage.

Her current CXR showed multiple ill-defined nodular lesions in the bilateral lungs (Figure 1), which were not found in the CXR 1 year ago. The lung nodules were identified in the CXR taken 3 months ago, but were much smaller. Chest CT revealed multiple flame-shaped, ill-defined solid nodular lesions, surrounded by ground-glass opacity (Figure 2). Based on the imaging and clinical findings, malignancy with lung and bone metastasis was considered first. The differential diagnosis included primary lung cancer, pulmonary lymphoma, pulmonary KS, fungal infection, pulmonary tuberculosis, and other atypical pneumonia.

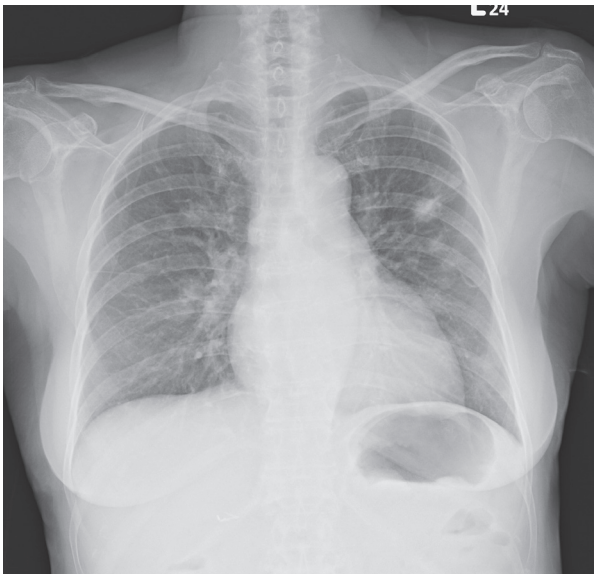

Fig. 1. CXR showed ill-defined nodular lesions in bilateral lung fields.

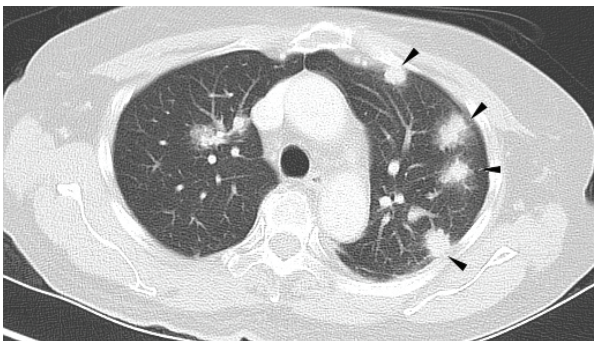

Fig. 2. Chest CT showed multiple flame-shaped, ill-defined solid nodular lesions, surrounded by ground-glass opacity (arrowhead).

Pathological examination of the tissue sample from bone obtained during vertebroplasty revealed no evidence of malignancy. Considering their peripheral distribution, a CT-guided biopsy of the lung lesions was performed. Initial pathological diagnosis was solitary fibrous

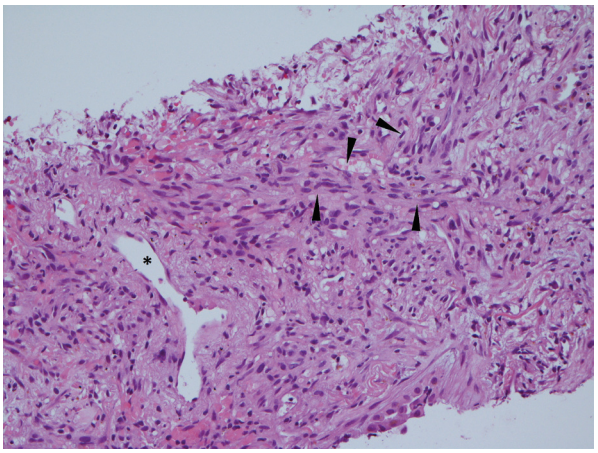

Fig. 3. H&E staining of lung lesion showed hypercellular fibrous tissue with haphazardly arranged spindle cells (arrowhead) and staghorn blood vessels (asterisk) (200X).

tumor, based on the hypercellular fibrous tissue with haphazardly arranged spindle cells and staghorn blood vessels that were seen (Figure 3). As the diagnosis was not compatible with the radiographic findings, additional pathological review and immunohistochemical staining were performed. The tumor cells appeared to be negative for STAT6 and positive for ERG1 and HHV8 (Figure 4). The pathological finding and immunohistochemical profile then led to the diagnosis of pulmonary KS.

After diagnosis, the patient received 2 cycles of systemic chemotherapy with tri-weekly

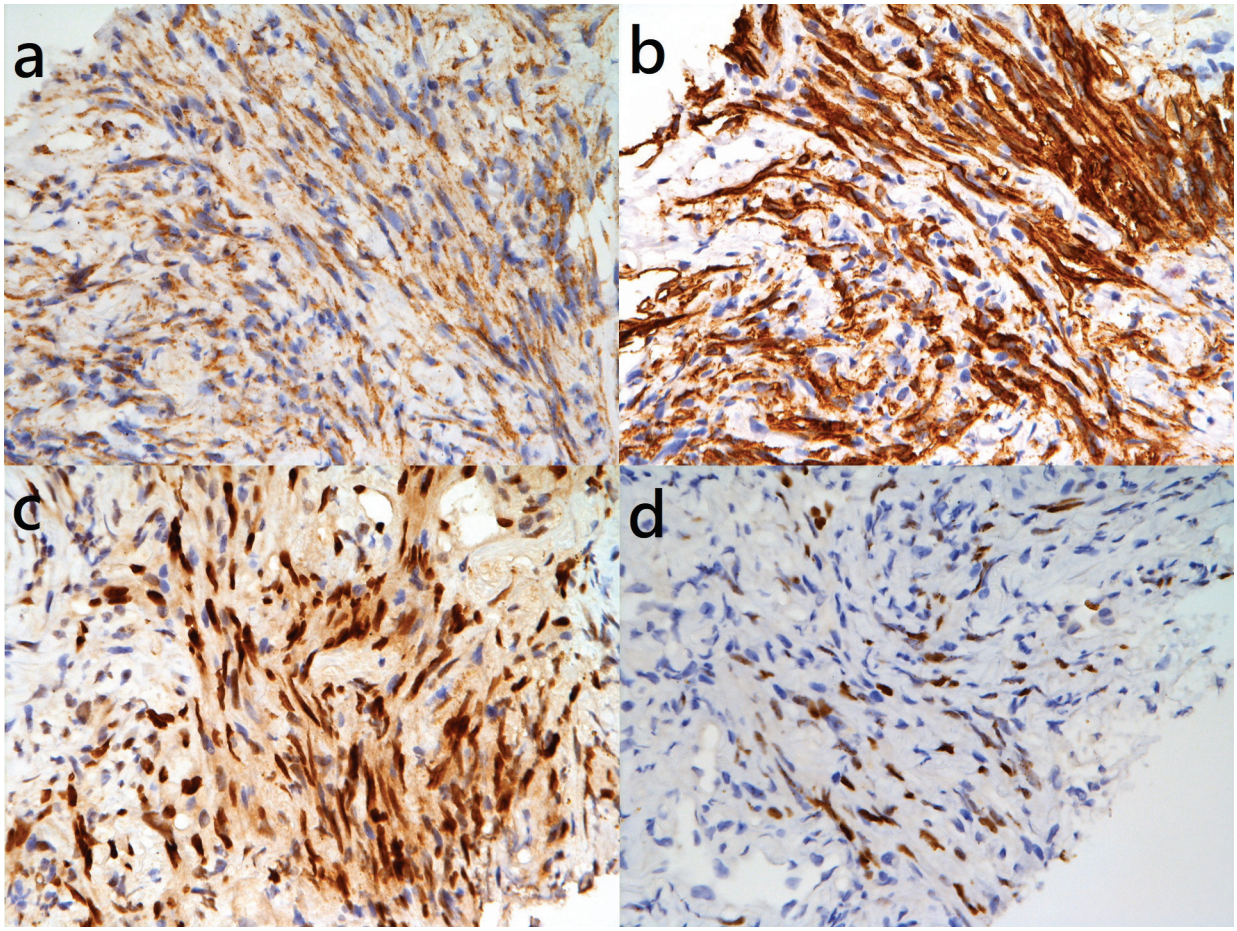

Fig. 4. Tumor cells were shown to be negative for STAT6 (a) and positive for CD34 (b), ERG1 (c) and HHV8 (d) (400X).

pegylated liposomal doxorubicin. Adjustment of the immunosuppressant for MG was also tried by the neurologist, but the patient could not tolerate it, as dyspnea developed soon after each adjustment. Pancytopenia followed by *Proteus mirabilis* bacteremia and cytomegalovirus colitis with viremia developed soon after the second cycle of chemotherapy. After stopping chemotherapy, the tumor progressed rapidly, and the patient ultimately died from respiratory failure 6 months after the diagnosis of KS.

Discussion

KS was first reported by Hungarian dermatologist Moritz Kaposi, who described the disease as "idiopathic multiple pigmented sarcoma of the skin" in 1872 [1]. KS is an angioproliferative tumor caused by infection with HHV8 [2], and is widely known as an AIDS-related malignancy.

Since HHV8 DNA can be isolated universally from KS tumor cells and the incidence of KS is higher in areas with a greater prevalence of HHV8 infection, HHV8 has been suggested to be a key factor in the development of KS [3-4]. However, the oncogenesis of KS involves a complicated reaction comprising inflammatory cytokine secretion and an impaired immune function that is unable to control the spreading of HHV8. The true role of HHV8 in the oncogenesis of KS is not well understood [4].

There are at least 4 forms of KS [5]: (1) classic KS, which occurs in elderly males with Mediterranean, Arabian or eastern European Jewish backgrounds; (2) endemic KS, which occurs in all age groups in equatorial Africa; (3) immunosuppression-associated, or iatrogenic KS, which affects patients receiving immunosuppressants, especially after solid organ transplantation; and (4) AIDS-associated KS, which is an AIDS-defining illness. The latter 2 forms are opportunistic diseases that affect immunocompromised persons, while the former 2 forms occur among healthy, immunocompetent persons without known precipitating factors. Classic KS is a rare disease, with an incidence rate of 0.3 per 100,000 persons per year in Europe [6]. The incidence rate is 400- to 500-fold higher in post-transplant patients [7]. In a review article, immunosuppression-associated KS accounted for 5.7% of de novo malignancies affecting organ allograft recipients [8]. We still know little about immunosuppression-associated KS, even though it is much more common than classic KS, and knowledge about its diagnosis and treatment is adopted mainly from AIDS-associated KS.

Among the immunosuppressive agents, calcineurin inhibitors (CNIs), including cyclosporine and tacrolimus, are considered to carry a higher risk of developing immunosuppression-associated KS [9-10]. There are also reports suggesting that azathioprine, which our patient was prescribed for MG, is associated with several malignant diseases, including KS [11].

Cutaneous disease is the most common presentation of KS. The skin lesions vary from macules and plaques, to nodules, with a purple, red, or brown color due to their vascular nature. Pulmonary involvement of KS is a rare condition in classic KS and immunosuppression-associated KS, but is common in AIDS-associated KS. Approximately 45% of patients with AIDS-associated KS were found to have pulmonary KS [5], but the percentage in autopsy data was much higher [12]. Isolated pulmonary KS without cutaneous lesions is less common [13-15]. About 85% of pulmonary KS patients had evidence of mucocutaneous involvement at the

time of diagnosis [14].

Common symptoms of pulmonary KS include cough, dyspnea, fever, chest pain, and hemoptysis [14-15]. The symptoms are nonspecific, and are difficult to distinguish from those of opportunistic pulmonary infection, which is also common in HIV-infected patients and those receiving immunosuppressants.

Pulmonary KS presents varied findings on CXR. The initial findings may manifest as nodules with a bronchovascular distribution or reticular opacities in the middle or lower lung field. Other possible findings include linear opacities, Kerley B lines, peribronchial cuffing, consolidation, pleural effusion, and intrathoracic adenopathy. The CXR finding may also be normal. The findings beyond common manifestations, including diffuse or apical opacity and cavitation lesions, should raise a suspicion of accompanying opportunistic infection, rather than KS alone [5,14-15].

Chest CT is a better diagnostic tool for pulmonary KS than CXR. Characteristic findings of pulmonary KS on CT include bilateral, roughly symmetrical, ill-defined nodules with a peribronchovascular distribution ("flame-shaped lesions"), often surrounded by ground-glass opacity ("halo sign"), and thickening of the interlobular septa. Other common findings on chest CT include pleural effusion and axillary, mediastinal, or hilar lymphadenopathy. A large lung mass, consolidation, and pleural implants are less common findings [5,16].

Although pleural effusion is a common finding in chest images, cytology of pleural fluid or histopathology of pleura biopsy samples typically is not useful in the diagnosis of pulmonary KS. Therefore, the main role of thoracentesis and pleural biopsy is to exclude other causes of pleural effusion, including infection and malignancy [17].

Bronchoscopy may be helpful in making the differential diagnosis. Endobronchial lesions of pulmonary KS are typically macular or papular lesions with a purple or bright red color. The lesions are usually flat or slightly raised, resembling the lesions seen in cutaneous KS [13,16]. While the finding of typical endobronchial lesions under bronchoscopy strongly suggests KS, transbronchial or endobronchial biopsies have a low diagnostic yield rate with a high risk of significant bleeding [16]. Bronchoalveolar lavage (BAL) may also be performed for patients with respiratory symptoms or abnormal chest image findings. Pulmonary hemorrhage caused by KS may be detected by BAL [14]. Diagnosis of KS cannot be made using the cytology specimens from BAL alone, but the BAL samples are useful in detecting pulmonary diseases other than KS. Polymerase chain reaction (PCR) can have 100% sensitivity and 98% specificity in detecting HHV8 DNA in specimens from BAL [18].

The differential diagnosis of pulmonary KS includes lymphoma, bronchogenic carcinoma, opportunistic pulmonary infection, and bacillary angiomatosis [5]. Malignant diseases are difficult to differentiate from benign diseases by imaging study alone, and biopsy is usually needed for a definite diagnosis [5]. Some image findings are uncommonly seen in pulmonary KS, including a tree-in-bud pattern, a nodular lesion less than 1 cm in diameter or with centrilobular distribution, a lack of pleural lesions or lymphadenopathy, and cavitary lesions. A diagnosis of infection should be considered with these findings [5]. Bacillary angiomatosis is a form of angiomatosis affecting primarily immunocompromised persons and is associated with *Bartonella* species. Bacillary angiomatosis may mimic KS with its similar appearance of cuta-

neous and endobronchial lesions, and it may also cause multiple pulmonary nodules and mediastinal lymphadenopathy, as seen on chest CT [19]. The diagnosis of bacillary angiomatosis can be made by histopathological examination, and the bacteria can be visualized with Warthin-Starry silver stain [19-20]. Although isolating *Bartonella* from a tissue sample is difficult, detection of *Bartonella* DNA in a tissue sample using PCR is also diagnostic for bacillary angiomatosis [20].

Clinical diagnosis of pulmonary KS can be made if typical endobronchial lesions are confirmed by bronchoscopy, with clinical and radiographic findings suggesting pulmonary KS. Lung biopsy may be performed to make the diagnosis if there are no endobronchial lesions or if the clinical or radiographic findings are atypical. The pathological features of KS include an aggregation of spindle cells which stain for CD34, angiogenesis with irregular vascular slits, and variable inflammatory mononuclear cell infiltrates [9]. Detection of HHV8 DNA by PCR or immunohistochemical staining of the biopsy sample can confirm the diagnosis [21].

While AIDS-associated KS may respond well to combination antiretroviral therapy, immunosuppression-associated KS also responds to a reduction or discontinuation of the immunosuppressive regimen. Switching the immunosuppressive regimen from CNIs to sirolimus or mycophenolate mofetil also has yielded benefits in some studies [10]. Systemic chemotherapy is indicated when there is rapid progression of disease, when the disease does not regress spontaneously after adjusting the immunosuppressive regimen, or when adjusting the immunosuppressive regimen is contraindicated clinically. Doxorubicin or daunorubicin is recommended as first-line treatment for AIDS-associated KS [22]. Although following the treatment guideline for AIDS-associated KS is suggested, the choice of a first-line treatment for immunosuppression-associated KS is unclear, as tumor response to other chemotherapy agents, including vinca-alkaloids, paclitaxel, and etoposide, also has been reported [23].

Compared with AIDS-associated KS, classic KS and immunosuppression-associated KS have a better prognosis in general, with less organ involvement and a better response to treatment [23-24]. Pulmonary involvement of KS, on the other hand, indicates a poor outcome, with a lower 5-year overall survival rate (49%) than non-pulmonary KS (82%) [25]. Patients with pulmonary involvement of KS may die from respiratory complications such as upper airway obstruction, hemorrhage, or parenchymal destruction, but the majority of deaths are caused by concomitant infection [26].

In conclusion, the possibility of pulmonary KS should be considered in immunocompromised patients with newly developed pulmonary lesions and without evidence of infection. Flame-shaped nodular lesions with a halo sign on chest CT support the diagnosis of KS, which can be confirmed by direct visualization of endobronchial lesions under a bronchoscope or by detecting the presence of HHV8 in a pathological sample. Immunosuppression-associated KS may regress spontaneously after reduction or discontinuation of the immunosuppressive regimen, and systemic chemotherapy is suggested when the disease does not response or the patient cannot tolerate adjustment of the immunosuppressive agents. In our case, long-term use of azathioprine and prednisolone and typical chest CT image findings led to a suspicion of KS. The diagnosis was confirmed by positive HHV8 immunohistochemical stain-

ing of the pathological specimen. Our patient unfortunately could not tolerate adjustment of the immunosuppressant regimen and died due to complications that developed soon after systemic chemotherapy.

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接受免疫抑制劑之重症肌無力病人的肺部卡波西氏肉瘤：病例報告

張均輔　黃煦晴　葉奕成 *　邱昭華

對於接受免疫抑制劑的病人而言，原發於肺臟的卡波西氏肉瘤是一不常見且不易診斷的併發症。我們報告的這位六十二歲女性因為重症肌無力症在接受免疫抑制治療十年後發生了肺部卡波西氏肉瘤，並且沒有皮膚侵犯。此診斷是以典型的肺部影像學、組織病理學表現和人類疱疹病毒第八型的免疫染色呈現陽性而確立。病患在接受了兩次全身性化學治療之後發生了菌血症和巨細胞病毒感染，並在診斷卡波西氏肉瘤六個月後死於呼吸衰竭。*(胸腔醫學 **2019; 34: 20-27**)*

關鍵詞：卡波西氏肉瘤，人類疱疹病毒第八型，硫唑嘌呤

臺北榮民總醫院　胸腔部，* 病理檢驗部
索取抽印本請聯絡：邱昭華醫師，臺北榮民總醫院　胸腔部，台北市石牌路二段 201 號

Acute Respiratory Failure Caused by Coexistence of Lymphoma and Pulmonary Tuberculosis: A Case Report

Yu-Ting Lai, Jyh-Pyng Gau*, Chung-Wei Chou**

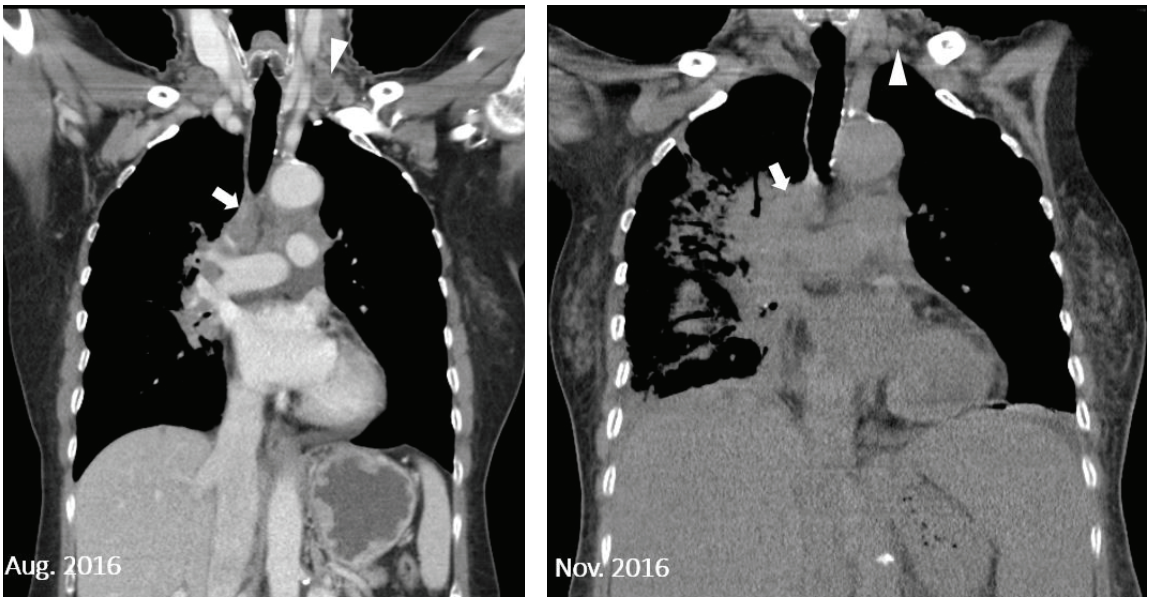
Mycobacterium tuberculosis (TB) is associated with a variety of clinical presentations, and lymphadenopathy (LAP) is a major manifestation of extrapulmonary TB. Here, we described the case of a 70-year-old woman who presented with pulmonary TB along with LAPs in 2 regions: the neck and the mediastinum. Tuberculous lymphadenitis was confirmed by neck lymph node biopsy. Although the neck LAP responded well to anti-TB therapy, the lung lesions and mediastinal LAPs progressed rapidly, leading to acute respiratory failure. Peripheral T cell lymphoma involving the lungs was later diagnosed. The patient was finally liberated from the mechanical ventilator after chemotherapy. Delayed diagnosis of either disease would account for the misleading manifestations and rare disease combination. In addition to clinical awareness, a distinct computed tomography enhancement pattern of LAP can also help in differentiating the 2 entities. An early diagnosis is critical to reducing or avoiding complications. ***(Thorac Med 2019; 34: 28-33)***

Key words: Mycobacterium tuberculosis, lymphoma

Introduction

Mycobacterium tuberculosis (MTB) and lymphoma can share common symptoms, such as loss of weight, fever, cough or the presence of lymphadenopathy (LAP). Concomitant presentations of TB and lymphoma are rarely reported, and the similarity in manifestations may lead to misdiagnosis or delayed diagnosis. Pulmonary TB presenting with mediastinal LAPs in adults is uncommon [1], and tissue sampling of the mediastinal LAPs is warranted for a definite diagnosis. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is less invasive than mediastinoscopy, but some patients may be unwilling to go through with the procedure, even though it is safe and well tolerated [2]. Also, there are no specific radiographic features of lymphoma on computed tomography (CT) scan [3], which increases the difficulty of diagnosis.

Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; *Division of Hematology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; **Division of General Chest Medicine, Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Chung-Wei Chou, Division of General Chest Medicine, Department of Chest Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd., Beitou District, Taipei 11217, Taiwan, ROC



(A) (B)

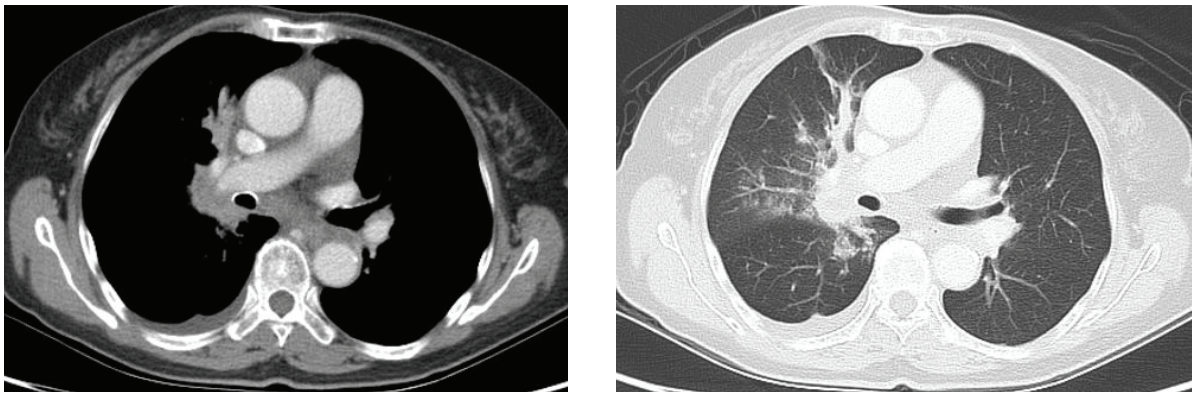
Fig. 1. Initial lower neck LAPs had peripheral enhancement (A, arrowhead); 3 months after taking anti-TB drugs, mediastinal LAPs (B, arrow) had enlarged, but neck LAPs regressed. (B, arrowhead)

Case Report

This 70-year-old female presented with chronic cough and weight loss of 4 kg during a 2-month period, beginning in June 2016. Meanwhile, several firm but non-tender nodules were also found at the left supraclavicular fossa. Chest CT on Aug. 13, 2016 showed bilateral lower neck LAPs with peripheral enhancement (Figure 1-A arrowhead) and homogenous mediastinal LAPs encasing the right main bronchus, along with infiltration at the right lung extending along the bronchovascular bundles and interstitial thickening (Figure 2). Excisional biopsy from the left neck LAPs showed chronic granulomatous inflammation with caseous necrosis and presence of acid-fast bacilli. Tuberculous lymphadenitis was confirmed by real-time polymerase chain reaction (PCR) assay and the sputum culture yielded MTB. EBUS-TBNA for mediastinal LAPs was therefore postponed because of the diagnosis.

The patient was admitted on Oct. 3, 2016, 2 months after initiating anti-TB therapy, due to nausea, jaundice and worsening right lung infiltration. In addition to giving her empirical antibiotics for suspected aspiration pneumonia, attempts were made to mitigate the adverse effects by withholding isoniazid and replacing it with levofloxacin and streptomycin. The pulmonary infiltration, however, progressed rapidly within the following 3 weeks, despite the use of broad-spectrum antibiotics. She was soon intubated because of acute respiratory failure.

Non-contrast chest CT was arranged on Nov. 2, 2016, given her worsening breathlessness, and revealed regressive change in the pre-existing neck LAPs and progressive, enlarged mediastinal LAPs (Figure 1), along with increased right-lung patchy consolidations and



(A) (B)

Fig. 2. CT on Aug. 2016 showed confluent LAPs at the mediastinum (A); thickening of the bronchovascular bundles and interstitial thickening. (B)

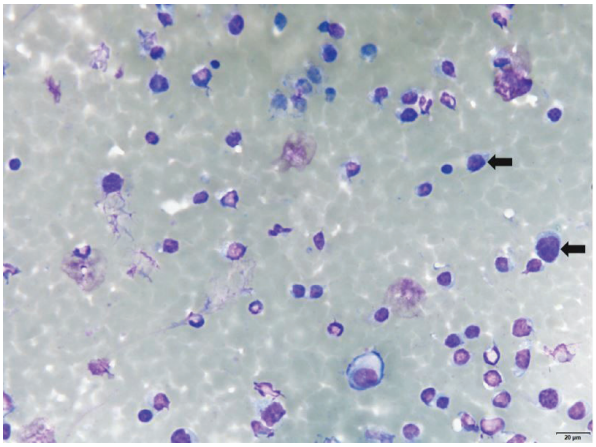


Fig. 3. Atypical lymphocytes (arrow) with high N/C ratios were found in the pleural effusion. (400X)

newly developed ascites and pleural effusion. Numerous atypical lymphoid cells with a high nuclear:cytoplasmic (N:C) ratio (Figure 3) were identified in the pleural effusion cytology. Cell block from the ascites depicted lymphoid cells positive for CD3 (Figure 4), suggesting a T cell origin. Peripheral T cell lymphoma was confirmed by bone marrow biopsy, which was immunoreactive for CD2, CD3, CD5, and CD25.

Chemotherapy with an initial reduced dose of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) was begun immediately in parallel with anti-TB drugs, beginning on Dec. 1, 2016. The pulmonary infiltration and mediastinal LAPs resolved gradually after 3 cycles of chemotherapy, and successful ventilator weaning was accomplished on Dec. 22, 2016.

Discussion

MTB is a widespread infectious disease that has been the focus of much attention in public health. With aggressive epidemic monitoring and effective treatment modalities, substantial progress has been made during the past decade in Taiwan, and the incidence rate has been lowered by one-third [4]. However, TB remains an issue among people possessing certain risks, such as HIV, having undergone organ transplantation, or chronic kidney disease [5].

A nationwide population-based study [6] conducted in Taiwan found a significantly higher TB incidence among cancer patients, especially those with head and neck cancer or

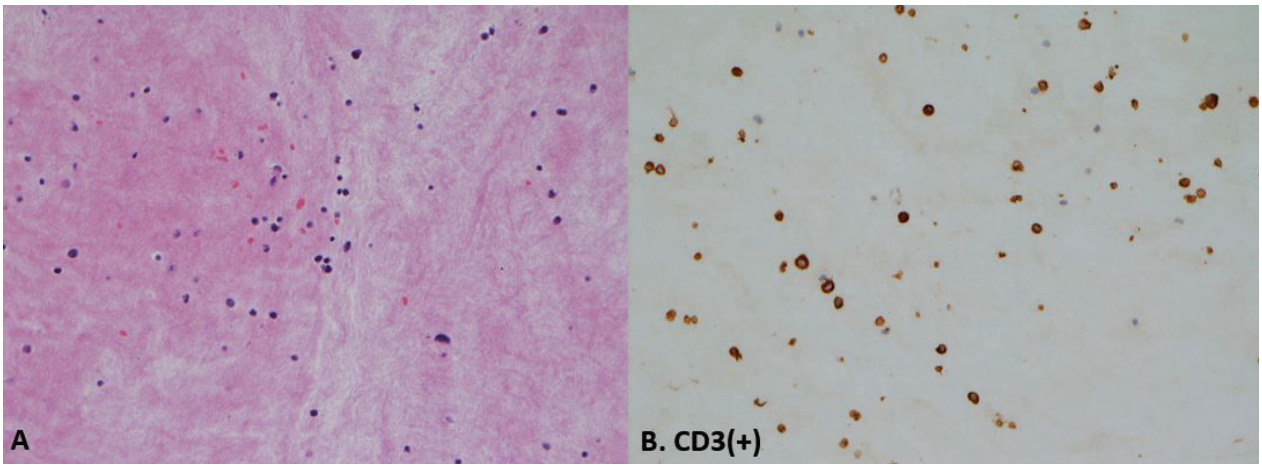


Fig. 4. Cell block from ascites under H&E stain (A); cells in IHC stain were positive for CD3 (B). (100X)

hematologic malignancy. Another study [7] concluded that patients with hematologic malignancy who develop extrapulmonary TB have higher 30-day in-hospital mortality. These results could possibly be explained by the use of robust chemotherapy to suppress the immune system or the cancer itself, which impairs the patient's immunity.

Despite numerous studies addressing the high incidence of TB in cancer patients, the concomitant occurrence is rarely reported. Tsai [8] presented 2 cases with coexistence of pulmonary TB and lymphoma involving the lungs, a condition that could be misleading and delay the diagnosis of either disease. Since chemotherapy could adversely worsen TB, and treating TB first would delay treatment for lymphoma, timely and concomitant treatment is crucial.

Lymphadenopathy is another manifestation of both TB and lymphoma, yet clinical and radiographic differentiation between the 2 can be challenging. Yang [9] and colleagues retrospectively reviewed the CT enhancement pattern of 69 patients (26 with TB and 43 with lymphoma) involving abdominal lymph nodes. They concluded that TB adenopathy commonly has significant peripheral enhancement and a multilocular appearance, while lymphoma has homogenous attenuation. The radiographic pattern of mediastinal lymph nodes showed similar results in a retrospective review of 40 patients in another study [10].

The aforementioned radiographic features could also be seen in our case. The LAPs with peripheral, multinuclear enhancement (Figure 1-A, arrowhead) at the left neck regressed after 3 months of anti-TB therapy, while the LAP with homogenous attenuation at the mediastinum progressed (Figure 1-B, arrow) during the same period. The contradictory treatment results implied that the LAPs in the mediastinum were of different disease entities.

Pathology, rather than the radiographic pattern, is the gold standard to differentiate pulmonary TB and lymphoma involving the lungs. The role of EBUS-TBNA in diagnosing lymphoma in the lung is still uncertain [11], given the paucity of published literature and the bias introduced in retrospective studies. Though some promising results have been reported [12], the inherent limitations of EBUS-TBNA,

such as low-volume samples and lack of tissue architecture, hinder its use in some subgroups of lymphoma. In spite of the controversial diagnostic value, the cytologic and pathologic specimen could still substantiate a suspicion of lymphoma.

This case reminds us that sometimes 1 disease may hide another, hence the clinician may be deceived in his reasoning for a straightforward diagnosis. TB and lymphoma can be causatively related due to the immunosuppressive effect [13]. The risk factor of TB in this patient was not obvious, and should be rigorously sought in patients. The mediastinal lymphadenopathies in an older patient such as ours, along with the paradoxical response to anti-TB drugs, should also raise a suspicion of malignancy. With clinical awareness, followed by scrutinizing the radiographic pattern and an aggressive diagnostic strategy, the patient could be freed from a delayed diagnosis of either disease.

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同時發生肺結核與淋巴癌所致急性呼吸衰竭－病例報告

賴俞廷　高志平 *　周中偉 **

結核病具有多樣的臨床表現，而淋巴結病變是其中一種。本文章探討一位七十歲婦人同時表現左頸淋巴結與縱膈淋巴結腫大。頸部淋巴結經切片證實為結核性淋巴腺炎後開始抗結核治療；雖左頸淋巴結經結核藥物治療後縮小，但肺部病灶與縱膈淋巴結仍持續惡化終至急性呼吸衰竭。經進一步檢查後證實肺部病灶為 T 細胞淋巴癌；病人也在化學治療後成功脫離呼吸器。這個病例說明淋巴結核與淋巴癌同時發生會讓臨床醫師在診斷過程中有誤解並致延遲診斷；除了臨床警覺外，文獻也提到二者的淋巴結病變在電腦斷層顯影形態上的不同可有助鑑別。雖然類似案例極少，但及時診斷才能減少併發症。*(胸腔醫學 **2019; 34: 28-33**)*

關鍵詞：結核病，淋巴癌

臺北榮民總醫院　胸腔部，* 臺北榮民總醫院　內科部血液腫瘤科，** 臺北榮民總醫院胸腔部　一般胸腔科
索取抽印本請聯絡：周中偉醫師，臺北榮民總醫院　胸腔部　一般胸腔科，臺北市北投區石牌路二段 201 號

Pulmonary Alveolar Proteinosis in a Patient with Hypocellular Myelodysplastic Syndrome – A Case Report and Literature Review

Yu-Chen Tsai*, Yi-Ting Chen**, Inn-Wen Chung*,***,****

Pulmonary alveolar proteinosis (PAP) is a rare lung disease with a variable clinical course characterized by abnormal surfactant-derived lipoprotein deposition. The cause of PAP might be congenital, secondary or acquired. Secondary PAP is often related to hematologic malignancy, the most common of which is myelodysplastic syndrome (MDS). Patients with hypocellular MDS have a survival rate superior to those with normo-/hyper-cellular MDS. However, the progression of PAP *per se* and PAP-associated infection may both contribute to a poor prognosis. We reported the case of a patient with hypocellular MDS with PAP presenting with recurrent pneumonia. ***(Thorac Med 2019; 34: 34-39)***

Key words: pulmonary alveolar proteinosis, myelodysplastic syndrome, hypocellular

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disease first described in 1958 [1]. It is characterized by a diffuse deposition of lipoproteinaceous material, primary surfactants, and surfactant apoproteins in the distal airways and alveoli. The clinical course is variable, ranging from self-limiting to respiratory failure [2]. Open lung biopsy is still the gold standard for reaching a diagnosis of PAP [3]. Herein, we present an uncommon case of PAP in a patient with hypocellular myelodysplastic syndrome (MDS).

Case Presentation

A 61-year-old housewife had a past medical history of pancytopenia with a hemoglobin level ranging from 5.5 to 9.1 mg/dL, and a peripheral blast percentage ranging from 0-5%. Dry tap occurred on a bone marrow aspiration in May 2005. She received a bone marrow biopsy again in May 2011, which revealed hypocellular marrow (cellularity was about 10-15%, hematopoietic elements were composed of a tri-lineage of hematopoietic cells) and positive immunoreactivity of CD34 and CD117 in myeloid cells with abnormal chromosomes (48, XX, dup(1)

*Division of Pulmonary and Critical Care Medicine, **Department of Pathology, Kaohsiung Medical University Hospital, and ***School of Medicine, ****Department of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
Address reprint requests to: Dr. Inn-Wen Chong, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan

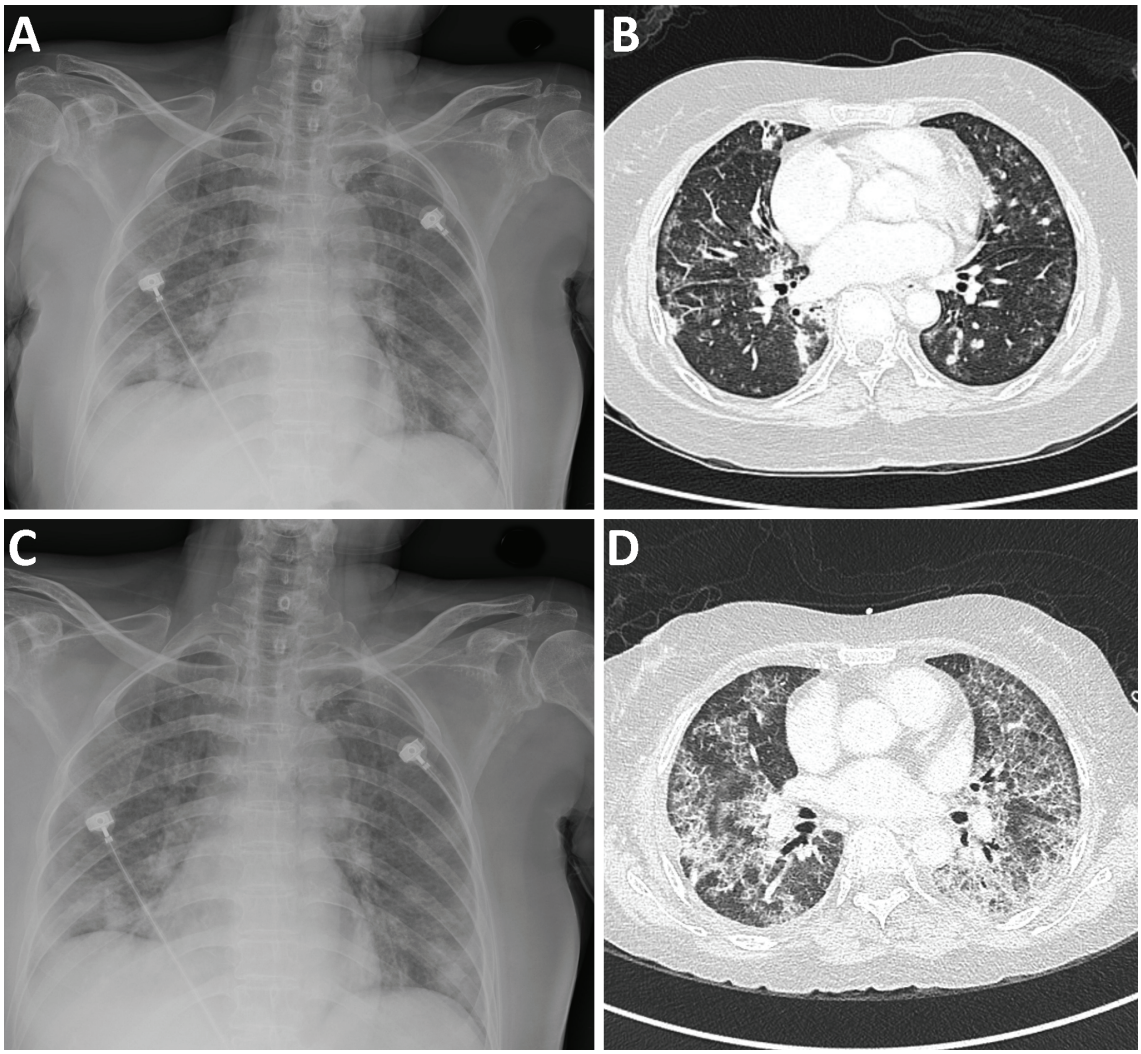

Fig. 1. Radiographic appearance of the patient in March 2014 and October 2014. The chest radiograph (A) and high-resolution computed tomography (CT) of the chest (B) disclosed a non-specific inflammatory process in both lungs. The follow-up chest radiograph 7 months later (C) showed the "bat wings" distribution and thin lucent bands which sharply outlined the diaphragm and heart. There was no evidence of cardiomegaly, lymphadenopathy, or effusion. The follow-up CT of the chest (D) showed a typical "crazy-paving" pattern characterized by ground-glass opacity with superimposed interlobular and intralobular reticular septal thickening.

(q12), +8, +9[16]/48, XX, +8, +9, add(10)(q24)[3]). Hypocellular MDS was diagnosed, and she received only supportive treatment with as-needed blood transfusion.

She had had several episodes of pneumonia with productive cough, high fever, and elevated C-reactive protein levels since June 2012. She also had frequent intensive care unit admissions due to respiratory failure and shock episodes. During an episode of pneumonia in March 2014 (Figure 1A), there was a delayed resolution of bilateral pulmonary infiltrates, so computed tomography (CT) of the chest was arranged, which revealed multiple consolidation patches, suggestive of an inflammatory process and septic emboli (Figure 1B). After prolonged

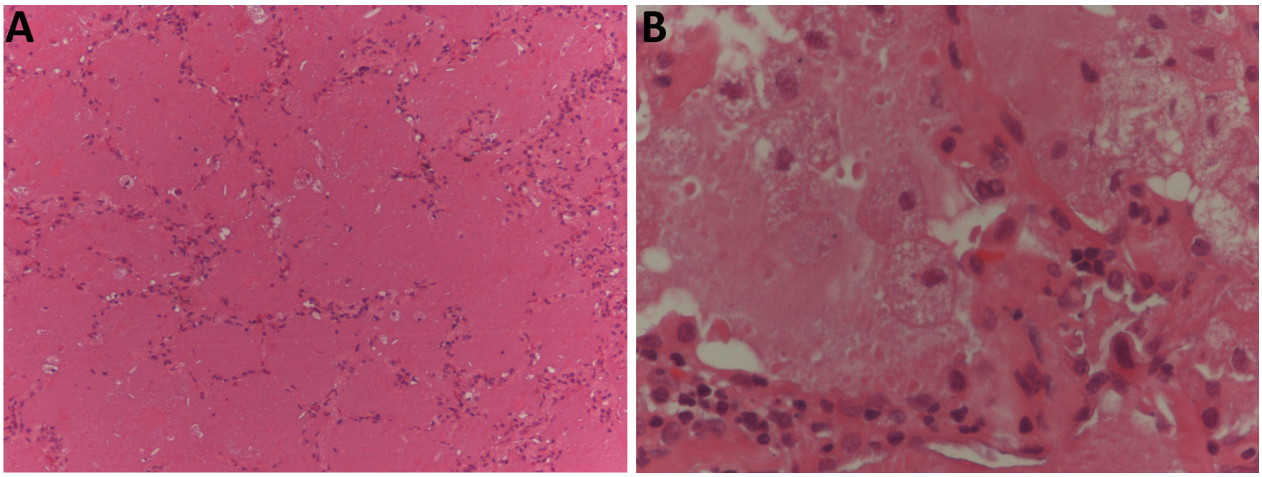

Fig. 2. Microscopic appearance with hematoxylin and eosin stain of the specimens from video-assisted thoracoscopic surgery (VATS) with wedge resection in October 2014. In the low-power field (A), relatively preserved alveolar architecture with lots of lipoproteinaceous materials accumulating in the alveolar spaces was noted. The high-power field (B) further revealed alveoli filled with amorphous, granular eosinophilic material, and foamy histiocytes.

antibiotic treatment, the patches improved partially. However, during another respiratory failure episode in October 2014 (Figure 1C), CT (Figure 1D) revealed a typical "crazy-paving" pattern characterized by ground-glass opacity with superimposed interlobular and intralobular reticular septal thickening. But the bronchoscopy revealed only tracheobronchitis with scanty sputum in the airway. To confirm the diagnosis of PAP, video-assisted thoracoscopic surgery (VATS) with wedge resection of the right middle lobe and right upper lobe was performed. The pathological examination of the specimens showed that the alveolar space was filled with amorphous or granular eosinophilic materials with minimal associated inflammation. Periodic acid-Schiff (PAS) stain highlighted the intra-alveolar granular materials, and no suspicious microorganism was disclosed by either PAS stain or Gomori methenamine silver stain. The diagnosis of PAP was made based on the pathologic characteristics of the specimens (Figure 2). Whole lung lavage was suggested after PAP was diagnosed, but the patient declined the suggestion due to an improving clinical course at that time.

Unfortunately, she developed respiratory failure again in November 2014, resulting in a requirement of prolonged mechanical ventilation support. Despite intensive care with broad-spectrum antibiotics and the performance of whole-lung lavage twice, she died of respiratory failure and septic shock in February 2015.

Discussion

Among adults with PAP, the typical age at presentation is 30 to 50 years, and there is a male-to-female ratio of 2:1 [4]. The major symptoms of PAP include progressive dyspnea on exertion, dry cough, fatigue, weight loss, and low-grade fever [3]. Typical laboratory abnormalities include polycythemia, hypergammaglobulinemia, and increased serum LDH level [5]. Serum LDH might correlate with disease severity [3].

PAP has 3 distinct forms: congenital (mutation in genes encoding surfactant proteins and granulocyte-macrophage colony-stimulating-factors [GM-CSF]), secondary (to immunosuppressants, hematological malignancies or toxic inhalations), and acquired or idiopathic (autoimmune disease, associated with GM-CSF autoantibodies). Secondary PAP is often related to hematologic malignancy, and MDS is the most common of these malignancies [6]. However, the pathogenesis of secondary PAP associated with MDS remains unclear. Most previous studies have shown that patients with hypocellular MDS (with <30% of bone marrow cellularity) have a survival rate superior to those with normo-/hyper-cellular MDS [7-8]. The duration from the diagnosis of MDS to the diagnosis of secondary PAP is longer in the group of MDS patients with a World Health Organization classification-based prognostic scoring system (WPSS) score of 0-1 than in those with a higher WPSS score, but the survival probability is similar after the diagnosis of secondary PAP, regardless of the MDS severity. The major causes of death are respiratory failure or infections associated with secondary PAP, rather than MDS *per se*. The presence of the cellular surface markers CD34 and CD117 is also associated with a shorter overall survival among these patients [9-10].

Both the progression of PAP *per se* and PAP-associated infection may contribute to the poor prognosis [11]. In secondary PAP associated with hematological diseases, a decreased number and impaired function of alveolar macrophages, which may be related to their origin from a malignant clone with a defective GM-CSF signaling pathway, has been observed [12]. Due to the presence of GM-CSF autoantibodies, impaired antimicrobial functions were noted in neutrophils from patients with PAP [13]. A meta-analysis of 410 PAP cases revealed that the increased number of infections in PAP may be related to a wide variety of pathogens, including bacteria, fungi, and other opportunistic microorganisms [14].

The natural history of PAP shows a high rate of spontaneous remission. Among symptomatic patients, longer disease duration is more likely to contribute to progressive disease [3]. Whole lung lavage is the most widely accepted and effective form of treatment for PAP with moderate-to-severe symptoms and hypoxemia. In the majority of reported cases, significant clinical improvement is usually achieved after whole lung lavage. Approximately 15% of patients have a relapsing course, requiring repeated procedures [15].

In conclusion, we reported an uncommon case of hypocellular MDS with recurrent pneumonia as the initial presentation of PAP. This case reminds us that PAP should be considered in a patient with hematological malignancy presenting with recurrent pneumonia.

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一名低細胞性骨髓化生不良病人的肺蛋白質沉積症－病例報告與文獻回顧

蔡毓真 * 陳怡庭 ** 鍾飲文 *,***,****

肺蛋白沉積症是一少見但病程歧異的肺部疾病。肺蛋白沉積症有三種不同的形式：先天型、續發型、及後天型。而續發型肺蛋白沉積症常與血液惡性疾病有關，其中以骨髓化生不良症候群最為常見。於骨髓化生不良症候群的病患中，低細胞性的患者通常有較好的預後。但肺蛋白沉積症的進展本身或其相關的感染皆會導致較差的預後。在此，我們報告一位低細胞性的骨髓化生不良症候群患者反覆表現肺炎，最後藉胸腔鏡生檢診斷為肺蛋白沉積症的病例。*(胸腔醫學 **2019; 34: 34-39**)*

關鍵詞：肺蛋白質沉積症，骨髓化生不良症候群，低細胞性

* 高雄醫學大學附設中和紀念醫院 內科部 胸腔內科，** 病理部，*** 醫學院醫學系，**** 呼吸治療學系
索取抽印本請聯絡：鍾飲文醫師，高雄醫學大學附設中和紀念醫院 內科部 胸腔內科，高雄市 807 自由一路 100 號

Crizotinib Treatment Failure in a Patient with Positive ALK-Rearranged Advanced-Stage Squamous Cell Lung Cancer – Case Report and Literature Review

Chin-Wei Kuo, Chi-Ho Wu*, Chang-Yao Chu**, Po-Lan Su, Chien-Chung Lin

In the era of target therapy, tyrosine kinase inhibitors are mainstream therapy for advanced-stage lung cancer with driver mutations present. Crizotinib has been documented to have a high overall response rate and good efficacy in the treatment of anaplastic lymphoma kinase (ALK)-rearranged advanced non-small cell lung cancer, as either first-line or rescue treatment. However, ALK rearrangement is rarely seen in lung squamous cell cancer. The overall response rate for crizotinib is uncertain, though some published case reports showed a positive response. Here, we present a case of positive ALK-rearranged advanced lung squamous cell cancer with a failed response to crizotinib treatment. ***(Thorac Med 2019; 34: 40-46)***

Key words: anaplastic lymphoma kinase (ALK), squamous cell carcinoma, crizotinib

Introduction

The rearranged anaplastic lymphoma kinase (ALK) gene was first reported as a fusion gene in anaplastic large-cell non-Hodgkin lymphoma in 1995. In 2007, Soda *et al*. first reported that the echinoderm microtubule-associated protein-like4 (EML4)-ALK fusion gene was an important oncogene in lung cancer [1-2]. EML4-ALK fusion genes are identified in approximately 5% of non-small-cell lung cancer (NSCLC) patients, a population of mostly adenocarcinoma patients among non-smokers (or light smokers) [2]. The first developed ALK inhibitor, crizotinib, had higher response rates and longer progression-free survival periods as first-line or second-line therapy than conventional platinum-based chemotherapy [3-4]. Patients with squamous cell carcinoma (SqCC) harboring an ALK rearrangement are extremely rare [5]. Experience in the treatment of ALK-positive NSCLC has involved mostly adenocarcinoma patients. The response rate of crizotinib in the treatment of lung SqCC is unknown at this time. Here, we present the case of a patient with ALK-rearranged advanced lung SqCC, who had no response to crizotinib treatment or to an attempt at rescue with combined immunotherapy

Division of Chest Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; *Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; **Department of Pathology, National Cheng Kung University Hospital, Tainan, Taiwan
Address reprint requests to: Dr. Chien-Chung Lin, Division of Pulmonary Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng-Li Rd. Tainan 704, Taiwan

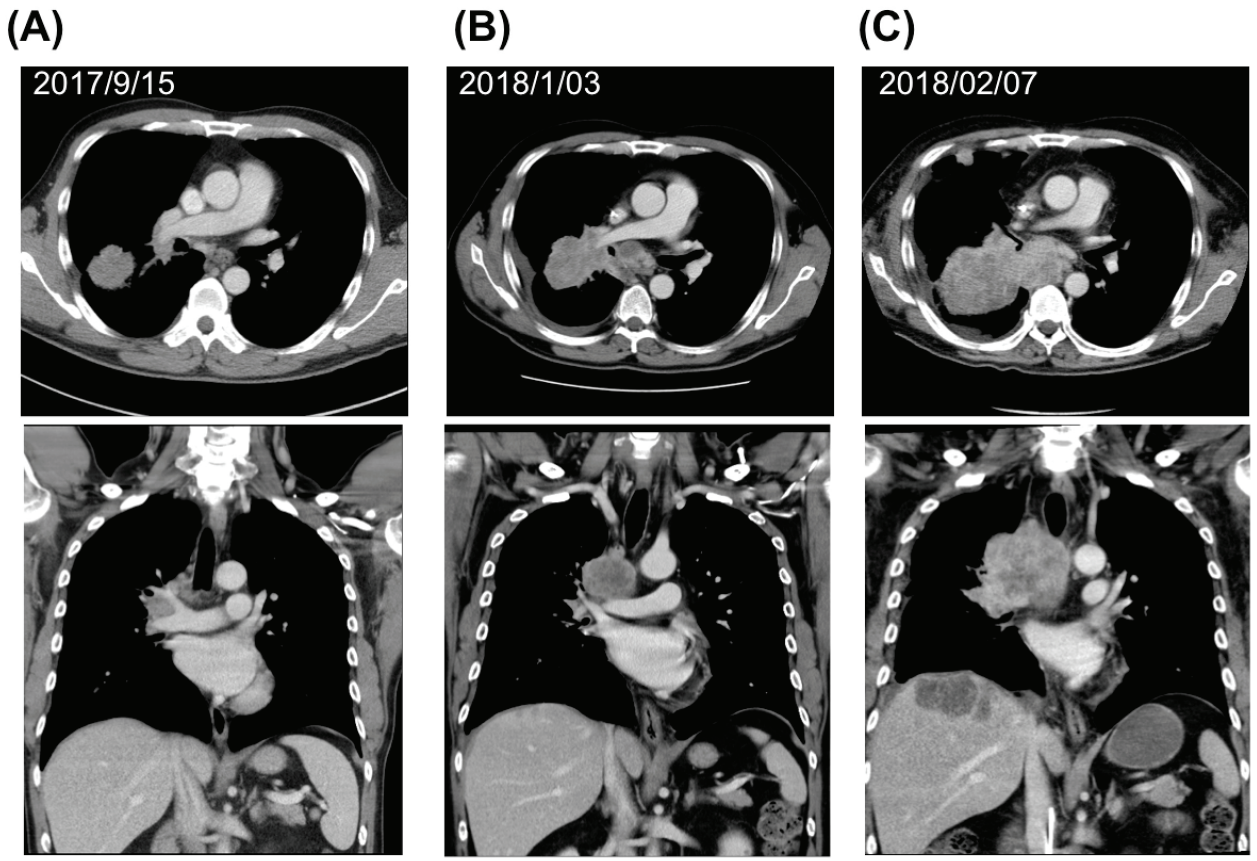

Fig. 1. Serial chest contrast CT scan showing changes in the patient's primary lung cancer and metastatic site from initial diagnosis (A), to after crizotinib treatment for 60 days (B), and after treatment with pembrolizumab combined with docetaxel (C).

and chemotherapy.

Case Report

A 50-year-old male without systemic disease presented intermittent hemoptysis for 1 month. He had smoked 1 pack of cigarettes a day for 30 years, and worked as an ice cube maker for decades. Initial chest computed tomography (CT) showed a 6.5-cm lung mass in the right lower lobe (RLL) with a satellite lesion and right pleura seeding (Figure 1). Endobronchial ultrasound-guided transbronchial needle aspiration and transbronchial lung biopsy were performed. SqCC was diagnosed by histopathologic morphology. Immunohistochemical (IHC) staining with p40 and cytokeratin was positive and transcription factor-1 was negative, which supported the diagnosis of SqCC. IHC staining (Ventana anti-ALK, D5F3) confirmed the presence of the ALK rearrangement (Figure 2). PD-1 immunostain (Clone: Dako, 22C3) confirmed a weak positive (20%) finding. EGFR mutation was not routinely performed. The patient was eventually diagnosed as having T3N2M1a (Stage IV) lung SqCC, according to the 7th edition of the American Joint Committee on Cancer staging system, on the basis of CT, bone scan, brain MRI, and pathological and immunohistochemical findings.

During first-line chemotherapy, the patient received 1,000 mg/m^2 of gemcitabine on day

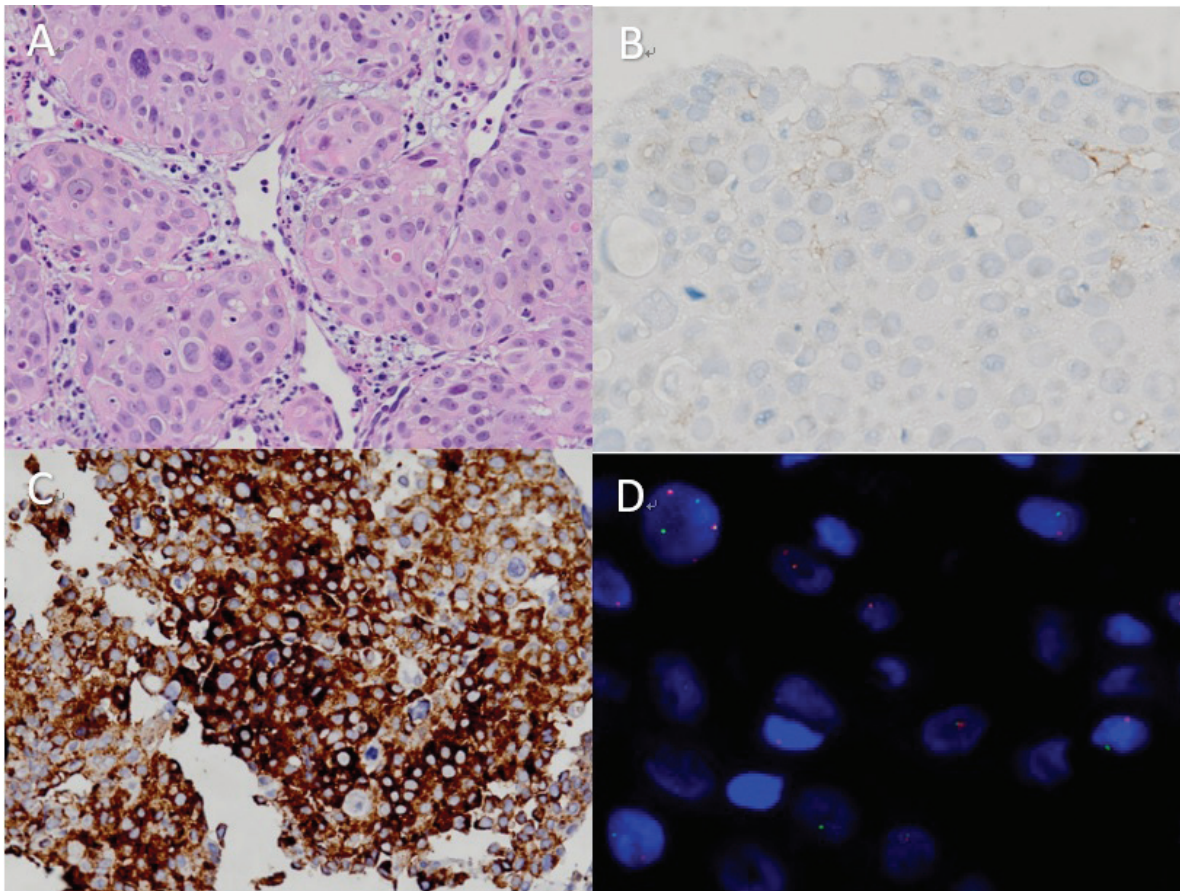

Fig. 2. Histopathological and immunohistological findings: (A) Hematoxylin and eosin stain revealing squamous cell carcinoma with moderate differentiation, (B) Immunostaining yielding low PD-L1 expression, (C) Anaplastic lymphoma kinase protein overexpressed, (D) Break-apart fluorescent in situ hybridization probe showing positive ALK rearrangement.

1 and day 8, and 60 mg/m^2 of cisplatin on day 1. Taiwan's National Health Insurance had not approved crizotinib at that time as first-line treatment for advanced stage NSCLC. Since the tumor showed no response to chemotherapy (Figure 1), we initiated crizotinib treatment at a dose of 250 mg, twice a day 28 days later. However, the patient suffered from chest pain with crizotinib treatment, and the chest CT image revealed an increase in the size of the RLL tumor after crizotinib treatment for 60 days. In addition, mediastinal lymphadenopathy and liver metastasis were found (Figure 1). Primary resistance to crizotinib was determined, and we discontinued use after a 75-day course of treatment. Since there is no standard treatment for patients with primary resistance to crizotinib, and chemotherapy remains the choice for patients who fail to respond to crizotinib, the patient was administered combination therapy with 100 mg of pembrolizumab plus 60 mg/m^2 docetaxol as third-line therapy. After the failure of crizotinib treatment, ALK fluorescent in situ hybridization (FISH) (Vysis ALK Break Apart FISH Probe Kit, Abbot Molecular) was performed to confirm the ALK rearrangement. The result was compatible with the IHC result (Figure 2). The patient did not respond to the first 2

Table 1. Literature Review of ALK-Positive Lung SqCC Responses to Treatment

Authors	Age(y)/ Sex	Clinical stage	Brain metastasis	ALK	Prior treatment	ALK inhibitor	Efficacy	PFS
Wang *et al* [7]	55 / F	T4N3M1(AJCC 6)	Negative	IHC, FISH	PDC	Crizotinib	PR	>11 weeks
Zhang *et al* [8]	55 / F	T1aN1M1b(AJCC 7)	Positive	IHC	PDC	Crizotinib	PR	24 weeks
Mikes *et al* [9]	36 / M	Stage IV	Negative	IHC, FISH, RT-PCR	None	Crizotinib	PR	>12 weeks
Vergne *et al* [10]	58 / F	Stage IV	Positive	IHC, FISH	PDC	Crizotinib	PR	30 weeks
Wang *et al* [11]	37 / F	Stage IV	Positive	IHC	PDC	Crizotinib	PR	36 weeks
Mamesaya *et al* [12]	52 / F	Stage IV	Negative	IHC, FISH	PDC	Alectinib	PR	44 weeks
Tamlya *et al* [13]	78 / M	No record	No record	IHC, FISH	None	Alectinib	PD	
Our case	50 / M	T3N2M1a (AJCC 7)	Negative	IHC, FISH	PDC	Crizotinib	PD	

ALK: anaplastic lymphoma kinase, AJCC: American Joint Committee on Cancer, F: female, FISH: fluorescence in situ hybridization, IHC: immunohistochemistry, M: male, PD: progressive disease, PDC: platinum-doublet chemotherapy, PFS: progression-free survival, PR: partial response, RT-PCR: reverse transcription-polymerase chain reaction, SqCC: squamous cell carcinoma.

cycles of combination therapy and his condition further deteriorated, so we switched our treatment to a second-generation ALK inhibitor, alectinib, at 600 mg BID. However, the patient died of cancer-related pulmonary embolism and obstructive pneumonitis after 3 days of alectinib treatment.

Discussion

It is estimated that 3-7% of patients with NSCLC, but only 1.3% of patients with SqCC of the lung will have an ALK rearrangement [6]. Previous studies showed an overall response rate of 65% among patients with ALK-positive NCSLC when using crizotinib as second-line treatment [3], and 74% when using it as first-line therapy [4]. However, the number of patients with ALK-positive SqCC enrolled in the above studies was very low. Thus, the actual response rate for crizotinib with ALK-positive SqCC is unknown. However, some reports have documented responses to ALK-inhibitors (Table 1), including crizotinib [7-11] and alectinib [12-13]. In the ALEX [14] and J-ALEX studies [15], alectinib showed superior efficacy and lower toxicity in primary treatment of ALK-positive NSCLC, compared to crizotinib. However, only 7 cases of SqCC were included in the ALEX study (2 in the crizotinib group and 5 in the alectinib group). In the J-ALEX study, 2 cases of SqCC (both in the alectinib group) were enrolled. No study compared overall response rates among ALK-positive SqCC patients treated with crizotinib or alectinib, since their population was small. For ALK-positive SqCC, the optimal ALK-TKI is still undetermined.

The incorrect identification of ALK translo-

cation or concomitant mutation may contribute to the poor response to ALK inhibitors among NSCLC patients. Some studies proposed a combination of the IHC and FISH algorithms for ALK testing, since the discrepancy between IHC and FISH is associated with different responses to ALK inhibitors [16-17]. Concomitant K-RAS mutation has been reported as a sign of primary resistance to crizotinib [18]. In our case, both IHC stain and FISH confirmed ALK rearrangement; therefore, a discordance-associated poor response to crizotinib could be excluded. However, the existence of a concomitant K-RAS mutation in this patient remained uncertain, since the residual tissue was not enough for further study.

The treatment strategy for patients with primary resistance to crizotinib is not yet established. According to National Comprehensive Cancer Network Guidelines, version 3, 2018, for NSCLC [19], the recommended choices after crizotinib treatment failure in patients with ALK-rearranged lung SqCC include systemic cytotoxic chemotherapy, immune checkpoint inhibitor, and second-line ALK inhibitors. The major problem is that the guidelines do not specify anything for patients with primary resistance to crizotinib. The CheckMate 057, KEYNOTE-010, and OAK trials reported a statistically significant improvement in overall survival (OS) with nivolumab, pembrolizumab, and atezolizumab treatment, respectively, over standard second-line docetaxel chemotherapy in patients with advanced NSCLC [20]. A recent meta-analysis of EGFR-mutant advanced NSCLC showed that immune checkpoint inhibitors did not improve OS more than docetaxel [21]. However, data on antitumor activity in the ALK-positive NSCLC subgroup of patients are incomplete. The combination of an immune checkpoint inhibitor with chemotherapy is another choice of treatment for advanced NSCLC. Checkpoint inhibitors work mainly on 'hot' tumors that have already been recognized by the immune system. In contrast, 'cold' tumors that have not been identified induce a failed response. By killing malignant cells with the combination strategy, chemotherapy generates an inflammatory response that draws T cells toward the cancer [21]. Current efforts are focused on new and potential combination strategies with synergistic antitumor activity. They use immune checkpoint blockade as a partner for chemotherapy with targeted agents [20]. However, our patient did not benefit from such combined treatment. Facchinetti *et al*. recently reported a patient affected by poorly differentiated lung adenocarcinoma harboring an ALK gene rearrangement. The patient did not respond to crizotinib, but subsequently benefited from treatment with ceritinib [22]. More molecular studies, such as next-generation sequencing, are needed to clarify who might benefit from other ALK-TKIs or next-generation ALK-TKIs, especially among SqCC patients harboring an ALK translocation.

Conclusion

ALK-positive lung SqCC is a rare entity in lung cancer. The overall response rate to ALK inhibitors remains undetermined. Though some patients benefit from crizotinib, the treatment strategy for those with primary resistance to crizotinib is still unclear. More clinical trials combined with recent methods in molecular biology are needed to clarify who would benefit from immunotherapeutic combinations or new-generation ALK-TKIs.

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Crizotinib 對於一位間變性淋巴瘤激酶重組的晚期鱗狀上皮肺癌病人的治療失敗－案例報告及文獻回顧

郭鈞瑋　吳啟豪 *　朱彰堯 **　蘇柏嵐　林建中

在標靶治療的時代中，酪胺酸激酶抑制劑是有驅動突變的晚期肺癌的治療主流。而 Crizotinib 已被證實對於有間變性淋巴瘤激酶重組的非小細胞肺癌病人在第一線或是後線的治療中，有一定程度的反應率和效果。可是，在鱗狀上皮細胞癌有間變性淋巴瘤激酶重組的比率非常低，雖然有少數病例報告顯示 crizitinib 對於此族群的病人有治療反應，但整體的反應率還無法確定。在此，我們提出一個個案報告，一位有間變性淋巴瘤激酶重組的晚期鱗狀上皮細胞肺癌的病人，在使用 crizotinib 治療後沒有反應且疾病迅速惡化。*(胸腔醫學 **2019; 34: 40-46**)*

關鍵詞：間變性淋巴瘤激酶重組，鱗狀上皮細胞肺癌，crizotinib

國立成功大學附設醫院　內科部　胸腔內科，* 國立成功大學附設醫院　內科部，** 國立成功大學附設醫院　病理部
索取抽印本請聯絡：林建中醫師，國立成功大學附設醫院　內科部　胸腔內科，台南市勝利路 138 號