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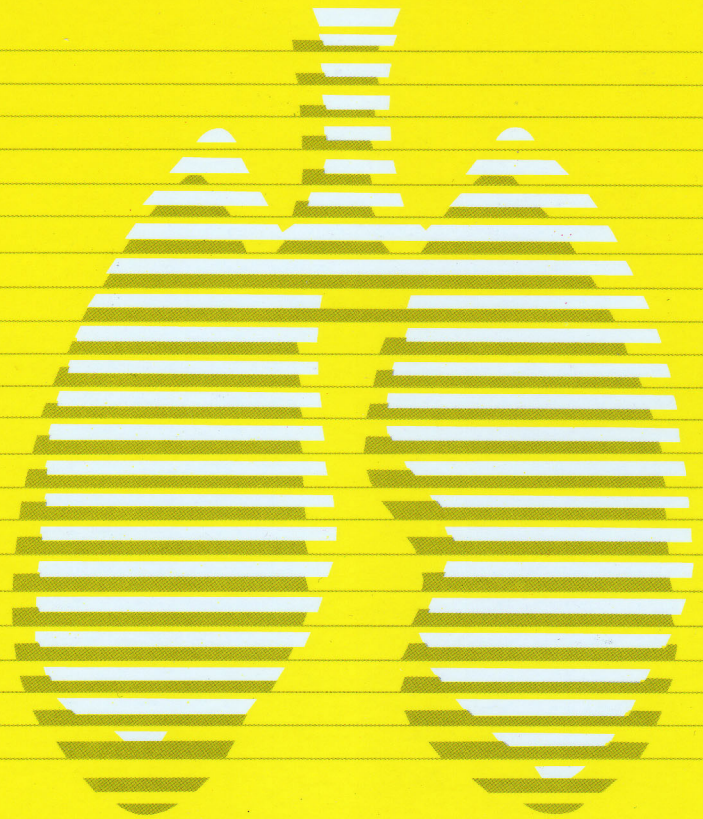

台灣胸腔暨重症加護醫學會

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原著

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Orginial Articles

Case Reports

Real-World Crizotinib Use for Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer under First-Year National Health Insurance Coverage in Taiwan

Yen-Ting Lin, Chung-Yu Chen, Jin-Yuan Shih*

Background: Crizotinib is effective in treating advanced non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) rearrangement [ALK(+)]. It has been approved by the National Health Insurance (NHI) administration in Taiwan for second-line treatment since September 2015. The clinical benefits and adverse effects of crizotinib in Taiwanese NSCLC patients have not yet been well investigated.

Patients and Methods: We enrolled patients who applied for NHI-covered crizotinib treatment for ALK(+) NSCLC from September 1st, 2015 to September 30th, 2016 at National Taiwan University Hospital. ALK gene rearrangement was detected by immunohistochemistry or fluorescence in situ hybridization. The patients' demographics, cancer status, crizotinib treatment response, drug-related adverse effects and survival were analyzed.

Results: Twenty-seven patients received crizotinib for ALK(+) advanced NSCLC during the study period. The tumor response rate was 26% and the disease control rate was 63%. The median progression-free survival (PFS) was 5.4 months; the median overall survival after crizotinib has not been reached yet. The PFS of patients with brain metastases before crizotinib treatment did not differ from the PFS of those without brain metastases. The crizotinib PFS between patients with brain progression and those with non-brain progression did not differ significantly. Nine (33%) patients were given a reduced dosage or discontinued crizotinib because of severe drug-related adverse effects.

Conclusions: In real-world practice, crizotinib is effective as a second-line treatment for advanced ALK(+) NSCLC. However, side effects are not uncommon. The response rate is lower and the PFS is shorter than that of clinical trial patients. ***(Thorac Med 2018; 33: 1-13)***

Key words: non-small cell lung cancer, ALK, crizotinib, brain metastasis, side effects, Taiwan

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Introduction

Crizotinib is an inhibitor of several receptor tyrosine kinases, including anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (c-Met) [1] and c-ros oncogene 1 [2]. ALK gene rearrangement (ALK positive [ALK(+)]) accounts for around 4% of all cases of non-small cell lung cancer (NSCLC) [3]. Fusing gene from the N-terminal domain of echinoderm microtubule-associated protein-like 4 (EML4) and the intracellular kinase domain of ALK results in constitutive activation of tyrosine kinase, leading to uncontrolled cell growth and proliferation [3]. Patients with ALK(+) NSCLC tend to be younger, light or never-smokers, and have the adenocarcinoma cell type [4]. Crizotinib is proven to be superior to chemotherapy for patients with ALK(+) advanced NSCLC. In the first- line PROFILE 1014 trial [5], crizotinib use led to longer progression-free survival (PFS) (10.9 vs. 7.0 months) and better overall response rate (ORR) (74% vs. 45%) than standard chemotherapy. In the second-line PROFILE 1007 trial [6], crizotinib use also resulted in longer PFS (7.7 vs. 3.0 months) and better ORR (65% vs. 20%) than chemotherapy. The U.S. Food and Drug Administration (FDA) has approved crizotinib as treatment for ALK(+) advanced NSCLC [7]. The National Health Insurance (NHI) administration in Taiwan has approved crizotinib as second-line treatment for ALK(+) advanced NSCLC since September 2015. However, the clinical effects and side effects of crizotinib in Taiwanese NSCLC patients are still not well known. Therefore, we analyzed our patients with advanced ALK(+) NSCLC treated with NHI-covered crizotinib.

Materials and Methods

Patients

This study retrospectively reviewed patients who applied for NHI-covered crizotinib for ALK(+) advanced NSCLC at National Taiwan University Hospital from September 1st 2015 to September 30th 2016. The patients were treated and followed up in accordance with their clinician's decision. Their serial images were checked, respectively, by an independent chest physician who was not involved in the care of any studied patient. Disease progression was defined according to RECIST criteria version 1.1 [8]. Patients' clinical characteristics, performance status using Eastern Cooperative Oncology Group (ECOG) criteria before crizotinib treatment [9], methods used to diagnose ALK(+), details of crizotinib treatment and clinical outcomes were recorded. Patients who never received crizotinib after NHI approval or who received crizotinib before September 1st 2015 were excluded. The latest follow-up day was March 8th 2017.

EML4-ALK fusion gene analysis

All patients underwent EML4-ALK fusion gene analysis before applying for NHI-covered crizotinib. We used D5F3 by Ventana for immunohistochemistry (IHC) staining. Fluorescence in situ hybridization (FISH) was used for diagnosis of some patients. The details were reported previously [10].

Statistical analysis

Continuous variables were reported as median with interquartile range (IQR). The Mann-Whitney U test was used as appropriate. Categorical data were compared using Fisher's exact test. Survival curves were plotted using

the Kaplan-Meier method and compared with the log-rank test. Statistical significance was set at $p<0.05$.

Results

Patient demographic and clinical characteristics

From September 1st 2015 to September 30th 2016, 32 advanced ALK(+) NSCLC patients applied for NHI-covered crizotinib at National Taiwan University Hospital. Three patients never received crizotinib after NHI approval (1 expired before approval; 1 received chemotherapy and the other refused crizotinib treatment); 2 patients that received self-paid crizotinib before NHI approval were excluded. In the end, 27 patients were included in further analysis. Most patients were never-smokers (n=17, 71%), had adenocarcinoma cell type (n=26, 96%), were diagnosed with ALK (+) by IHC (n=23, 88%) and had undergone 1 prior anticancer therapy regimen (n=16, 59%) (Table 1).

Crizotinib effectiveness

Of the 27 patients, 7 had a partial response (PR), 10 had stable disease (SD) and 10 had progressive disease (PD). The response rate (RR) was 26% and the disease control rate (DCR) was 63% (Figure 1). The median PFS was 5.4 months (95% confidence interval [CI], 4.7-6.1) (Figure 2A); the median overall survival (OS) has not been reached yet (Figure 2B). For the 16 patients who received crizotinib as second-line therapy (Figure 3), the RR was 31% and the DCR was 75%. Median crizotinib PFS was 7.0 months (95% CI, 2.9-11.1).

We further compared PFS and OS between patients with ECOG 0-1 and ECOG 2-4 on crizotinib day 1 (Supplementary Figure 1), and

Table 1. Demographics of Patients Receiving Crizotinib (n=27)

Age (years)	55 (IQR, 48-64, range 35-72)
Gender	Male, 17 (63%)
	Female, 10 (37%)
Smoking[1]	Never-smoker: 17 (71%)
	Current or ex-smoker: 7 (29%)
Cancer cell type	Adenocarcinoma, 26 (96%)
	Poorly differentiated carcinoma, 1 (4%)
Cancer status before crizotinib	Recurrence[2], 10 (37%)
	Stage IV, 17 (61%)
Diagnosis of ALK(+)[3]	IHC, 23 (88%)
	FISH, 3 (12%)
Prior anticancer therapy (line)	median, 1, (IQR 1-3, range 1-9)
ECOG before crizotinib	ECOG 0-1, 20 (73%)
	ECOG 2-4, 7 (26%)

Abbreviations: IQR, interquartile range; ALK(+), anaplastic lymphoma kinase gene arrangement; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ECOG, Eastern Cooperative Oncology Group

[1] 3 patients did not have smoking status data

[2] Recurrence refers to postoperative or post-concurrent chemoradiotherapy recurrence

[3] One patient referred from another hospital had no record of the ALK diagnosis method.

found there was no significant difference in PFS and OS between the 2 groups (PFS, median, 5.5 [95% CI, 3.1-7.8] months vs. 1.0 [95% CI 0.9-1.2], p=0.11; neither median OS in both groups has been reached yet, p=0.93). When analyzing PFS and OS between crizotinib as second-line treatment and third-or-more line treatment, we found trends that revealed PFS and OS might be better in the second-line group (median PFS, 7.0 [95% CI 2.9-11.1] months vs. 1.4 [95% CI 0-6.6] months, p=0.06, Supplementary Figure 2A; neither median OS in two groups has been reached yet, p=0.13, Supplementary Figure 2B).

Crizotinib and prior brain metastasis

Twelve patients (44%) had brain metastasis before crizotinib treatment. The baseline characteristics did not differ significantly between patients with and without brain metastasis before crizotinib (Supplementary Table). Among patients with prior brain metastasis, 8 (80%) had stable brain metastasis, 2 (20%) had progressed, and 2 others were not evaluable after crizotinib treatment. The crizotinib PFS between those with and without prior brain metastases did not differ significantly (median 5.5 [95% CI 0.4-10.5] months vs. 5.0, [95% CI 0-11.8] months, p=0.60, Supplementary Figure 3).

Disease progression

Seventeen (63%) patients had disease progression: 5 progressed in the brain only, 5 progressed in the lung or pleural effusion only, 2 progressed in the liver only and 1 progressed in the supraclavicular lymph node only. The 4 other patients had progression in multiple sites. The PFS for patients with and without brain progression did not differ significantly (median, 1.7 [95% CI: 0.1-3.3] months, vs. 1.4 [95% CI: 0-3.6] months, p=0.88, Supplementary Figure 4A). The OS between those with and without brain progression also did not differ significantly (median, not reached vs. 2.8 [95% CI: 0-11,

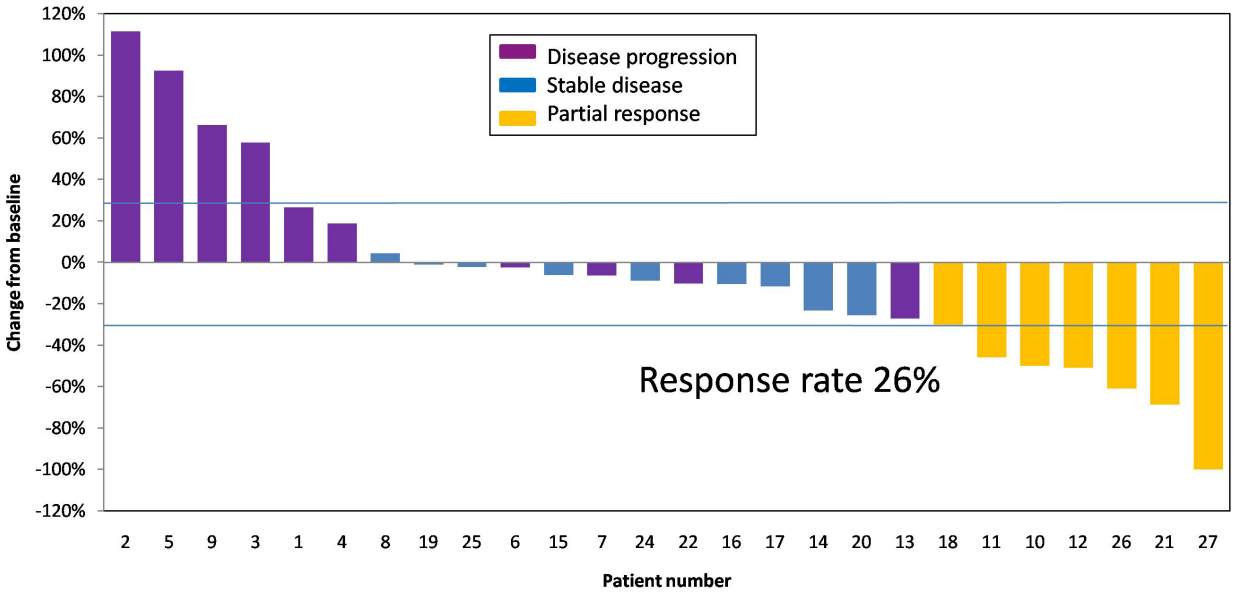


Fig. 1. Best response of targeted lesions by patient, based on maximal percentage of tumor change.

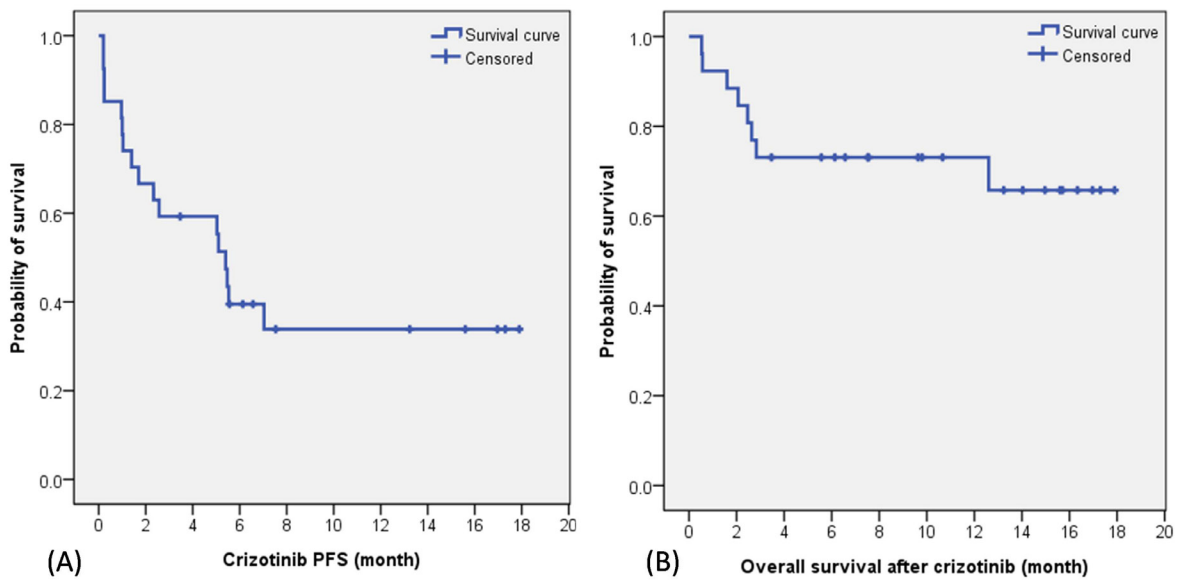


Fig. 2. (A) Crizotinib progression-free survival (PFS); (B) Overall survival (OS) after crizotinib treatment.

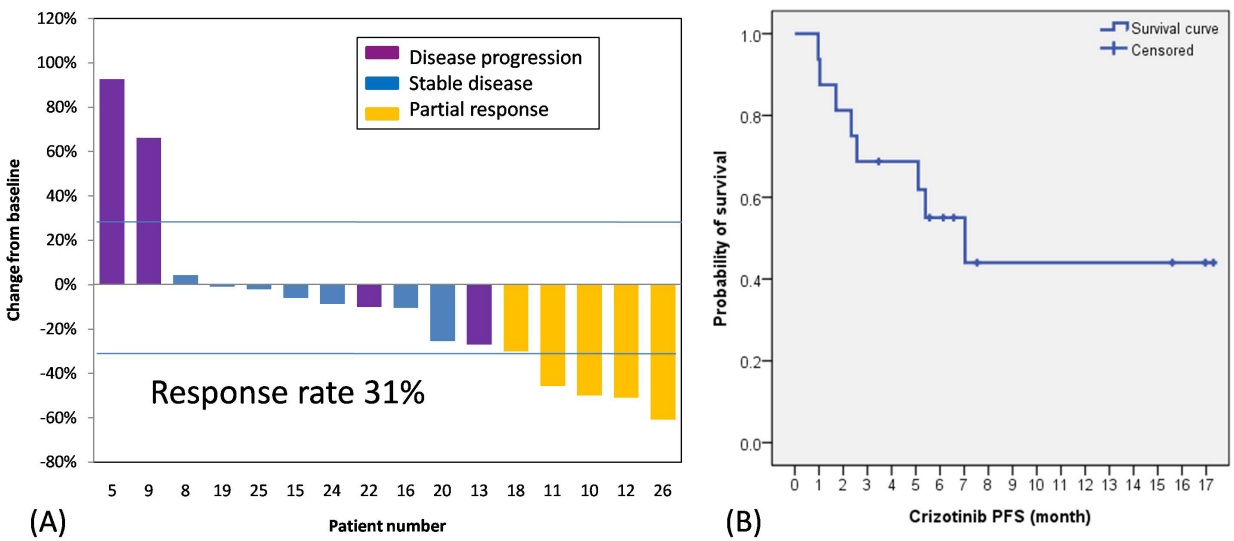


Fig. 3. (A) Best response of targeted lesions by patient, based on maximal percentage[,] for patients receiving crizotinib as second-line anticancer therapy; (B) Crizotinib progression-free survival (PFS) in patients receiving crizotinib as second-line anticancer therapy

8] months, p=0.16, Supplementary Figure 4B). Ten patients continued crizotinib beyond disease progression (Figure 4). The median crizotinib duration after progression was 51 (IQR 23-142, range 7-311) days; 4 of the 10 patients had progression in the brain, 2 in the lung, 2 in the liver, 1 in the supraclavicular lymph node, and 1 in both the liver and in malignant pericardial effusion. Of the 4 patients who had progression in the brain, 2 underwent cyberknife radiosur-

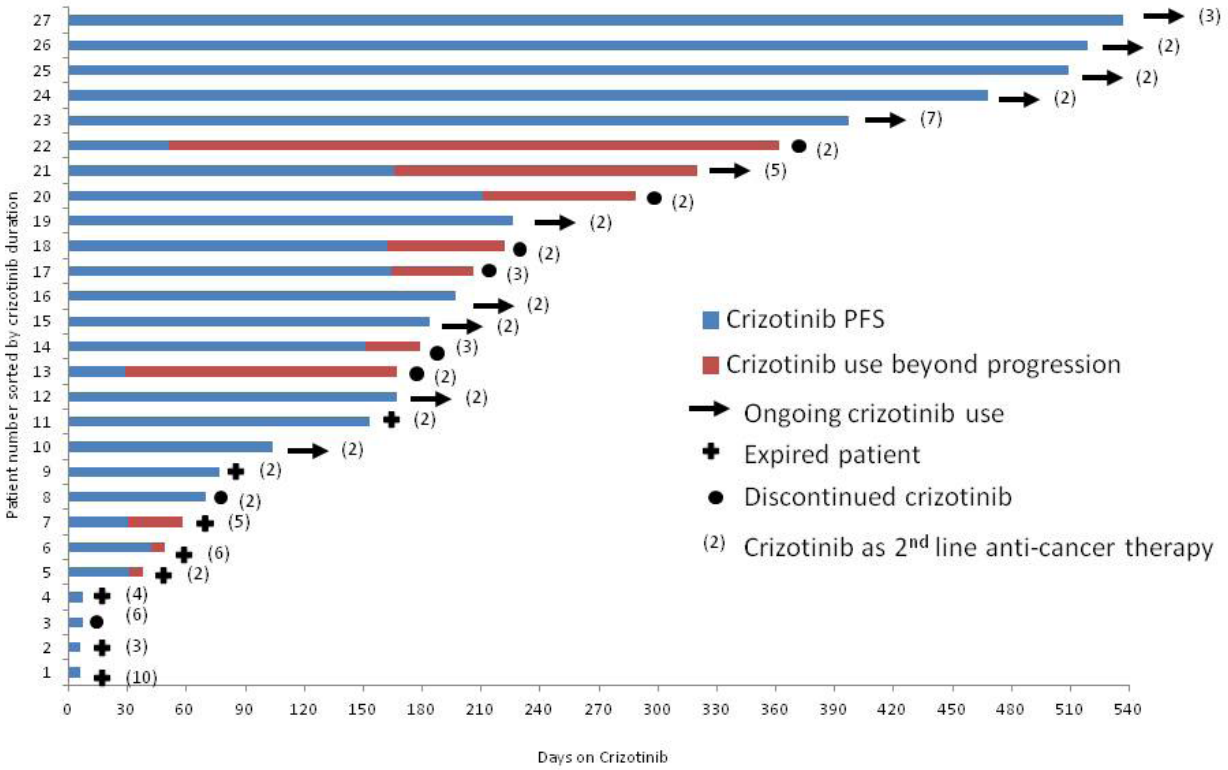


Fig. 4. Treatment timelines for all patients receiving crizotinib (n=27)

gery for local control (patient 13 and patient 22 in Figure 4) and 1 received whole brain radiotherapy (patient 21 in Figure 4).

Crizotinib side effects

Nine (33%) of the 27 patients had adverse effects leading to a decreased crizotinib dosage (n=6) or precluding further use (n=3) (Table 2). After a dose reduction, the 6 patients tolerated further crizotinib use. Two of the 3 patients that stopped crizotinib died soon after discontinuing the treatment; the other shifted to another treatment for lung cancer.

Discussion

We reported on real-world crizotinib use for advanced ALK(+) NSCLC in Taiwanese patients. The RR was 26% and the DCR was 63%. The median PFS was 5.4 months, but median OS after crizotinib was not reached. In all, 33% of patients had severe adverse effects leading to dose reduction or permanent discontinuation of crizotinib.

The RR and PFS in this study were lower than in previous clinical trials. According to PROFILE 1007 [6], crizotinib use in patients with an ECOG status of 0-2 who had previously failed 1 platinum-based chemotherapy regimen yielded longer PFS (7.7 vs. 3.0 months) and better ORR (65% vs. 20%) than either pemetrexed or docetaxel. After restricting our patients to second-line crizotinib only, our median crizotinib PFS was 7.0 months, similar to PROFILE 1007 (Figure 3), but the RR was still only 31%.

Table 2. Crizotinib Side Effects Leading to Decreased Crizotinib Dosage or Precluding Further Use (n=9)

Dose reduction	Patient numbers (reduced dosage)
Nausea and vomiting	3 (1#* Q.D.)
Leukopenia (ANC <1000) and GI symptoms	1 (1#* B.I.D./Q.D. alternatively)
Elevated transaminase	1 (1#* Q.D.)
Fluid retention	1 (1#* Q.D.)
Preclude further crizotinib use	
Severe nausea and vomiting	1
Acute pulmonary embolism	1
Suspected interstitial pneumonitis	1

*Crizotinib 1# = 250 mg

Abbreviations: Q.D., *quaque die* (once a day); B.I.D., *bis in die* (twice a day); ANC, absolute neutrophil count; GI, gastrointestinal

In our study, the PFS of patients with different ECOG performance statuses (ECOG 0-1 vs. ECOG 2-4) was not significantly different, although better performance tended to have longer PFS (Supplementary Figure 1). Performance status is traditionally a prognostic factor for cancer patients receiving chemotherapy [11]. In the era of targeted therapy, patients with a poor performance status may still respond well if a sensitive driver mutation is present [12]. Most of the patients experienced an improvement in performance status after treatment. A case study on a patient with advanced ALK(+) NSCLC reported dramatic improvement after crizotinib use [13], but this was a single case. Thus, performance status may not be an absolute prognostic factor for patients with a targetable driver mutation. Because of our limited patient numbers and follow-up time, further larger cohort studies are warranted.

PFS for second-line crizotinib tended to be longer than PFS for third-or-more line treatment in this cohort. A similar trend in OS was also found. This is reasonable because many patients in the third-or-more line crizotinib group were heavily treated - they received crizotinib as third- to tenth-line anticancer therapy. The failure of these patients may be due to a poor performance status when they received crizotinib, which is supported by similar Kaplan-Meier curves in Supplementary Figure 1A and Supplementary Figure 2A. They also may have been suffering from possible side effects of previous chemotherapy. Moreover, second-line crizotinib patients have more treatment options available, and OS may be better with third-or-more line crizotinib (Supplementary Figure 2B). The swimmer plot of the patients (Figure 4) may also partly explain the poorer RR and the shorter PFS in the cohort. Most patients that died shortly after crizotinib were heavily treated patients (patients 1, 4, 6, and 7 in Figure 4). These patients were not included in clinical trials. Most of the patients who received crizotinib as second-line therapy appeared in the upper part of the graph, indicating their longer PFS in Figure 3B. As the patient numbers increase and the follow-up time lengthens, more mature data will be available.

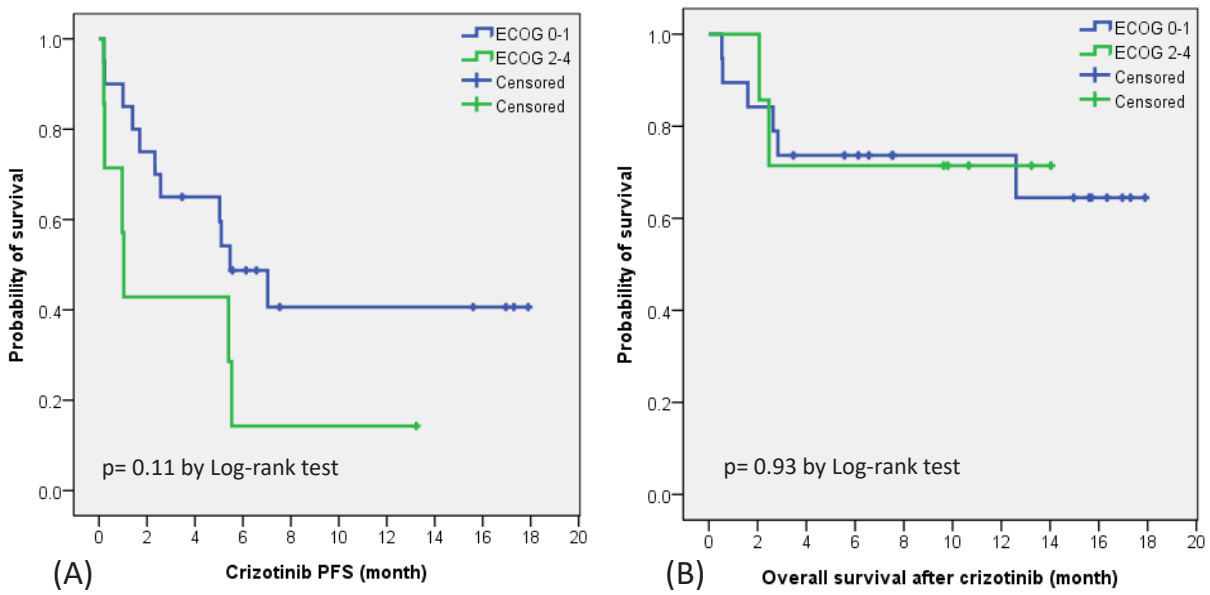
There are indeed differences between clinical trials and real-world practice. Among metastatic lung cancer patients, real-world practice

has significantly greater hospitalization rates [14]. In treatment for prostate cancer [15], colorectal cancer [16], glioblastoma [17], and lung cancer [18], real-world patients often do not obtain the same beneficial effect from treatment as trial patients do. Instead, they may suffer from more severe toxicity with similar regimens [14]. Clinical trial patients often are not the same population as general practice patients. The former are highly selected patients who tightly adhere to the study protocol. They are beneficiaries of more resources - not only the study drug but also more intensive monitoring for effects and side effects. Their treatments are more standardized. Non-compliant patients and difficult-to-treat patients, such as those at a very old age, with multiple comorbidities, and refractory to multiple previous treatments, are excluded. Therefore, real-world practice data may be as important as data from clinical trials [18].

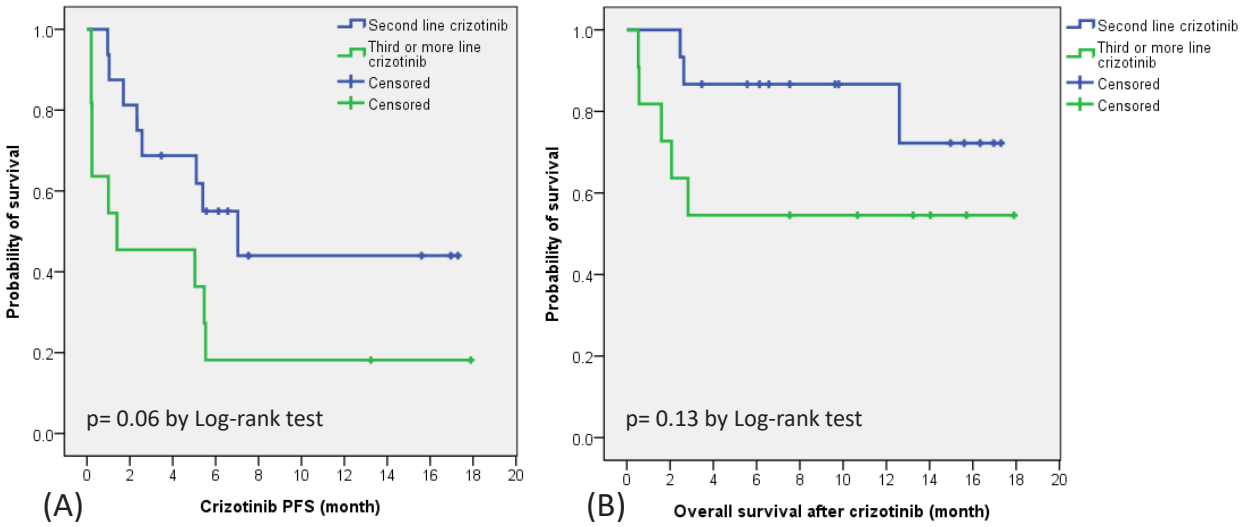
We found that crizotinib PFS did not differ between those with and without brain metastasis (Supplementary Figure 3). The clinical characteristics were similar, except that those patients with prior brain metastasis tended to have undergone more prior anticancer therapy (p=0.07) (Supplementary Table). There was also a tendency for those patients in this cohort with more prior anticancer therapy to have poorer crizotinib PFS (Supplementary Figure 2A). In spite of this disadvantage in baseline characteristics, patients with prior brain metastasis still had PFS that was comparable to patients without prior brain metastasis. These results are not consistent with the results of 2 recent studies from Japan (n=59) [19] and China (n=34) [20] that found that patients with prior brain metastasis had shorter PFS than those without. Our result may be due to our limited patient numbers (n=12) and shorter follow-up time. Similar to these 2 reports, the brain was the most frequent single metastatic site in our patients. However, the PFS between brain progression and non-brain progression did not differ significantly (Supplementary Figure 4A). Brain metastasis did not seem to be a major determent for the crizotinib effect in our patients. Furthermore, continuing crizotinib use beyond brain progression together with local radiotherapy for brain metastases seemed to be a reasonable choice, because sustained cancer control in other sites and prolonged survival may be possible (for example, patients 13, 21 and 22 in Figure 4). This effect was not seen in patients with single-lung progression or single-liver progression.

Intolerable gastrointestinal (GI) symptoms were the most frequent side effect in our patients, leading to dose reduction or precluding its further use. In phase III trials of crizotinib [5-6], the most common side effects were vision disorder (60-70%), diarrhea (60%), nausea and vomiting (around 50%), and constipation (40%). Grade 3 and 4 side effects were mainly GI problems (nausea, vomiting and constipation) and elevated aminotransferase. Our results were comparable to those of the clinical trials. One of our patients developed acute pulmonary embolism 7 days after crizotinib use. She had received 5 lines of anticancer therapy prior to crizotinib treatment, but the cancer was still progressing. She underwent a pulmonary endarectomy and survived. We could not find any report in the literature regarding the association between crizotinib and acute pulmonary embolism. Whether crizotinib caused the pulmonary embolism was uncertain, but crizotinib was suspended permanently in this patient.

There are limitations to this study. First, because of the rarity of ALK mutation in NSCLC

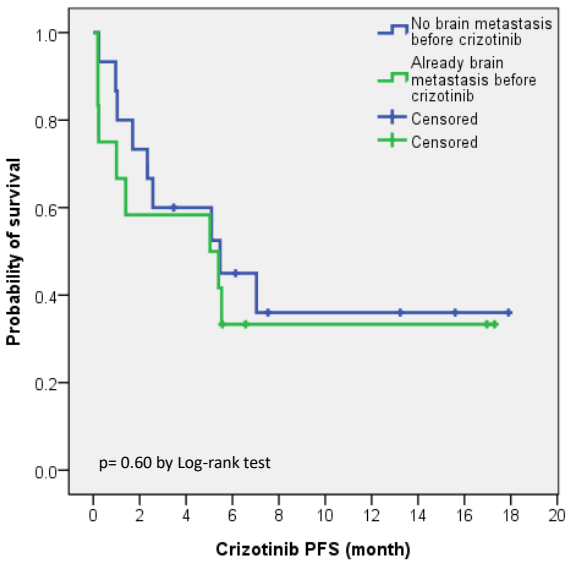


Supplementary Figure 1. (A) Crizotinib progression-free survival (PFS) and (B) Overall survival (OS) between ECOG 0-1 and ECOG 2-4 patients.



Supplementary Figure 2. (A) Crizotinib progression-free survival (PFS) and (B) Overall survival (OS) between second-line crizotinib and third-or-more line crizotinib patients.

patients and that ALK inhibitors have been covered by Taiwan's NHI for just over a year, the number of studied patients was small and follow-up time was short. As the patient numbers and follow-up time increase, more mature data will be available. Second, physicians may still

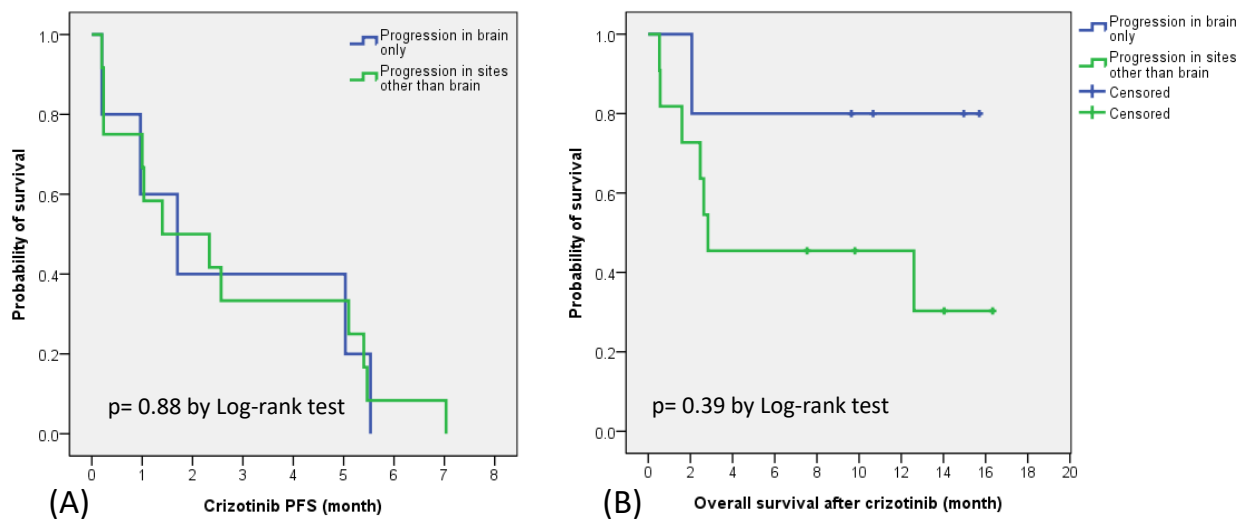


Supplementary Figure 3. Crizotinib progression-free survival (PFS) between patients with and without brain metastasis before crizotinib.

be "becoming familiar" with this "new drug," which may affect its performance. Third, many patients had been heavily treated and received crizotinib as salvage treatment. They may have received crizotinib when in a very poor performance status. Fourth, this is a single center's experience and the results might not be generalizable to all patients. However, to date, this is the first report of Taiwanese patients receiving crizotinib in real-world practice.

Conclusion

In real-world practice, crizotinib is effective as a second-line treatment for advanced ALK(+) NSCLC in Taiwanese patients. However, the response rate is lower and the PFS is shorter than among clinical trial patients. Side effects of crizotinib are not uncommon, as well.



Supplementary Figure 4. (A) Crizotinib progression-free survival (PFS) and (B) Overall survival (OS) between patients who progressed only to the brain and patients who progressed to other sites after crizotinib therapy.

Supplementary Table Clinical Characteristics of Patients with and Without Brain Metastasis (BM) Prior to Crizotinib

	Patients without prior BM (n=15)	Patients with prior BM (n=12)	*p*
Age (year-old)	61 (50-65)	55 (48-61)	0.41
Gender	Male, 11 (73%) Female, 4 (27%)	Male, 6 (50%) Female, 6 (50%)	0.26
Smoking[1]	Never smoker: 11 (85%) Current or Ex-smoker: 2 (15%)	Never smoker: 6 (55%) Current or Ex-smoker: 5 (45%)	0.35
Cancer status before crizotinib	Recurrence[2], 6 (40%) Stage IV, 9 (60%)	Recurrence[2], 4 (33%) Stage IV, 8 (67%)	0.51
Prior anticancer therapy (line)	1 (1-2)	2 (1-2)	0.07
ECOG before crizotinib	ECOG 0-1, 12 (80%) ECOG 2-4, 3 (20%)	ECOG 0-1, 8 (67%) ECOG 2-4, 4 (33%)	0.66

Abbreviations: BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group
[1]Total 3 patients in the two groups do not have smoking status data.
[2]Recurrence refers to post-operative or post concurrent chemoradiotherapy recurrence

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Crizotinib 在台灣健保給付的第一年於 ALK(+) 晚期非小細胞肺癌患者之使用

林彥廷　陳崇裕　施金元 *

前言：Crizotinib 可有效治療晚期有 ALK 基因重組 ([ALK(+)] 之非小細胞肺癌。2015 年 9 月起二線 crizotinib 治療已納入台灣全民健保給付，然而 crizotinib 在台灣健保病患的治療效果及副作用仍然尚不清楚。

方法：分析台灣台大醫院於 2015 年 9 月 1 日至 2016 年 9 月 30 日，申請使用全民健保 crizotinib 治療晚期 ALK(+) 非小細胞肺癌病患之臨床特徵、腫瘤狀況、crizotinib 治療的反應以及副作用。

結果：在研究期間總共有 27 位 ALK(+) 晚期非小細胞肺癌病患接受健保 crizotinib 治療，腫瘤的反應率為 26%，疾病控制率為 63%，中位數無病存活期 (PFS) 為 5.4 個月，中位數存活期 (OS) 則尚未達到。無論病患在 crizotinib 治療前有無腦部轉移，PFS 並無顯著差異；無論病患在 crizotinib 治療後無論是否發生腦部轉移，PFS 亦無顯著差異。有 9 位 (33%) 病患在治療中因為副作用需要減量或停藥。

結論：在現實臨床的病患，crizotinib 對台灣晚期 ALK(+) 非小細胞肺癌的病患是有效的二線治療。然而腫瘤反應率及 PFS 均較臨床試驗差，治療相關的副作用也不少見。*(胸腔醫學 **2018; 33: 1-13**)*

關鍵詞：非小細胞肺癌，ALK，crizotinib，腦轉移，副作用，台灣

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Concomitant Mycobacterium and Nocardia Bacteremia Presenting with Acid-Fast Bacilli-Positive Blood Smears: A Case Report

You-Lung Chang, Chien-Hong Chou

Mycobacterium tuberculosis infection is endemic in Taiwan, and an acid-fast bacilli (AFB) smear-positive specimen is a diagnostic reference for mycobacterium infection. Systemic mycobacterium infection or mycobacteremia will be suspected first if an AFB-positive blood smear is documented. Here, we report the case of a patient who had concomitant *Mycobacterium avium complex* and *Nocardia nova* bacteremia presenting with AFB-positive blood smears, and emphasize the importance of the differential diagnosis of a positive acid-fast stain. ***(Thorac Med 2018; 33: 14-19)***

Key words: mycobacterium, Nocardia, myasthenia gravis, bacteremia

Introduction

An acid-fast bacilli (AFB)-positive sputum smear is an important diagnostic reference for mycobacterium infection, which is endemic in Taiwan. With an existing AFB stain-positive blood smear, systemic mycobacterium infection or mycobacteremia is always given priority in the differential diagnosis. However, *Mycobacterium tuberculosis*, nontuberculous mycobacteria (NTM), Nocardia, Rhodococcus, Tsukamurella, Gordonia, *Legionella micdadei* and some protozoa such as Cryptosporidium, Cyclospora and Isospora may all stain positive for AFB [1]. Here, we report the case of a patient who had concomitant *Mycobacterium avium complex* and *Nocardia nova* bacteremia presenting with AFB-positive blood smears, and emphasize the importance of the differential diagnosis of a positive AFB stain.

Case Report

A 53-year-old man had underlying myasthenia gravis with thymoma status post-video-assisted thoracoscopic thymothymectomy, poliomyelitis with lower limbs contracture since childhood, hypertension and diabetes mellitus. He had been able to walk with a walker and led an independent life under titrated prednisone 30 mg and pyridostigmine for at least 3 years after the diagnosis of myasthenia gravis 6 years pre-

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vious. He suffered progressive limbs weakness, exertional dyspnea and dysphagia, accompanied with intermittent choking, poor appetite, and general malaise 1 month before this admission. He complained of diffuse abdominal pain, and was found to be drowsy and short of breath by his family on the day he was admitted to the emergency room. There was no fever, nausea/vomitus, cough, chest tightness, diarrhea, tarry/bloody stool passage, or back pain. At the emergency room triage, his consciousness level was E1V1M3. Vital signs were as follows: blood pressure: 94/34 mmHg, pulse rate: 111 beats/min, respiratory rate: 18 breaths/min, temperature: 36.9°C, and SpO_2: 88%. Physical examination showed an oval-shaped abdomen and rhonchi breathing sounds at the bilateral lung field. Laboratory data revealed leukocytosis with a left shift, metabolic acidosis, and impaired renal function. Chest X-ray showed bilateral decreased lung volume and increased infiltrates. Intubation was performed for acute respiratory failure and septic shock.

He was admitted to the ICU under the impression of a myasthenia gravis crisis with respiratory failure and septic shock, related to suspected pneumonia or intraabdominal infection. His consciousness became oriented and muscle power gradually recovered under plasma exchange used to counter a suspicious myasthenia gravis crisis, and continuous venovenous hemofiltration (CVVH) to treat refractory metabolic acidosis. On day 2, he was isolated due to a sputum smear revealing a positive acid-fast stain quantified as 1+. Computed tomography (CT) scan for infection survey later showed suspected perforation at the descending-sigmoid colon junction with focal abscess formation and right upper lobe and left lower lobe segmental atelectasis with pleural effusion, as well as left upper lobe patchy opacity (Figure 1). Surgical intervention with hemicolectomy and colostomy was then performed. On day 3, preliminary blood culture documented Gram-positive bacillus with a positive acid-fast stain. Pulmonary tuberculosis (TB) with mycobacteremia was highly suspected, but TB polymerase chain reaction (PCR) was negative. However, morphologically Gram-positive bacillus, possibly Nocardia species, was suspected after discussion with the laboratory staff. Combined treatment with imipenem and trimethoprim/sulfamethoxazole against suspected Nocardia bacteremia was administered right away. On day 7, sputum culture grew *Mycobacterium avium intracellulare* complex. On day 10, 3 sets of blood culture collected on day 1 grew *Nocardia nova*. The patient, however, passed away due to profound septic shock on day 11. On day 37, 1 set of blood culture grew *Mycobacterium avium intracellulare complex*.

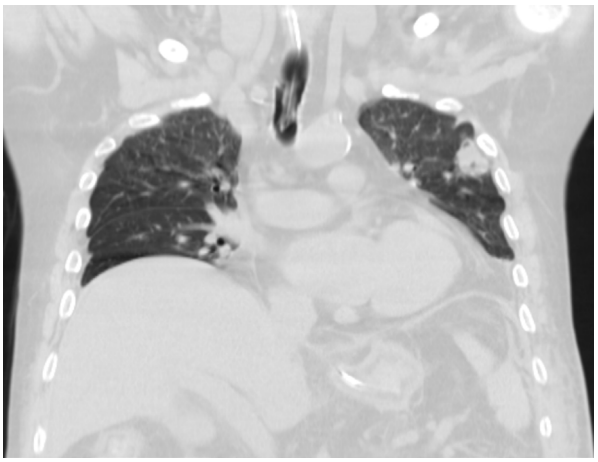

Fig. 1. Chest computed tomography showing right upper lobe and left lower lobe segmental atelectasis with pleural effusion, as well as left upper lobe patchy opacity.

Discussion

The genus Nocardia, a Gram-positive bacillus belonging to the suborder of "aerobic actinomycetes", dwells in water, soil and other decomposing organic matter. While immunocompromised patients are the major victims, about one-third of patients are immunocompetent [2]. There are more than 85 Nocardia species, among which, approximately 25 species are related to human infections, including *Nocardia asteroides complex, N. nova complex, N. transvalensis complex, N. brasiliensis, N. abscessus, N. pseudobrasiliensis, N. cyriacigeorgica, N. farcinica, N. veteran* and *N. cerradoensis*. The routes of transmission of Nocardia infection are usually through inhalation or via damaged skin, and the infection can then spread throughout the body, including the brain, heart, kidneys, joints and bones. Nocardia infection, though rare, can also develop due to nosocomial risk factors (e.g., a catheter or surgery)[3]. Lung disease is the most common manifestation of Nocardia infection and the central nervous system the most common extrapulmonary location [2,4]. The prognosis of systemic Nocardia infection is relatively poor, with a mortality rate ranging from 7% to 44%, and even up to 85% in severely immunocompromised patients [5].

Nontuberculous mycobacteria (NTM), also found in nature or in treated water and soil, are opportunistic pathogens, as well. They infect both immunocompromised and immunocompetent patients and, as with Nocardia, lung disease is the most common manifestation. *Mycobacteria avium intracellulare complex* (MAC) is the most common organism in NTM-related lung disease [6]. Systemic NTM infection has been significantly associated with high mortality, ranging from 30% to 71%, depending on the host immune status [7-8].

It is hard to differentiate Nocardia from Mycobacterium right away without molecular biology-based laboratory support, because clinically both present similarly: they both grow in a Mycobacteria Growth Indicator Tube (MGIT) and Löwenstein-Jensen medium, are stained using the Ziehl-Neelsen procedure and look similar in terms of colony morphology [9]. However, Nocardia exhibits weaker acid-fastness than *Mycobacterium tuberculosis* under a modified Kinyoun acid-fast stain with 1% sulfuric acid as a decolorizer, in contrast to the more potent hydrochloric acid in the Ziehl-Neelsen procedure; unlike mycobacteria, Nocardia has a beads-like acid-fast appearance on microscopy [2]. The macroscopic and microscopic presence of aerial hyphae is characteristic of Nocardia in the colonial morphology. This differentiates the genus Nocardia from other related genera, such as Rhodococcus, Gordona, Tsukamurella, Corynebacterium, and Mycobacterium [5]. Streptomyces and other aerobic actinomycetes members may grow aerial hyphae, but they all have negative acid-fastness [10]. Aerial hyphae on slow-growing Mycobacteria are never seen but mature colonies of some rapid growers, such as *M. xenopei*, may produce projections comparable to aerial hyphae [11]. Only experts can differentiate Nocardia from Mycobacteria filamentous branches [9]. A number of biochemical assays, such as LCN-A or TLC, were used in the past to differentiate Nocardia from Mycobacterium, but are not widely used nowadays [12-14]. The PCR technique is more sensitive than conventional methods in detecting Nocardia [15]. The use of PCR-RFLP (PCR-restriction fragment length polymorphism) analysis (PRA) to recognize and separate individual Nocardia and mycobacteria has been a recent focus of at-

tention [16-17]. Also, the PRA-hsp65 method with BstEII restriction site detection seems to be a promising assay [9,18].

Nocardia or NTM infection alone is common in immunocompromised patients, but coinfection with both species is rare. Some reports indicate that more than two-thirds of patients diagnosed with pulmonary nocardiosis were initially diagnosed as having TB, and about 5% of patients with proven pulmonary TB were shown to have co-infection with Nocardia [19-20].

In our patient, the lung may have been the source of systemic NTM infection, but the etiology of the disseminated *Nocardia nova* infection cannot be determined. Poor immune function due to long-term steroid treatment for myasthenia gravis may have led to multimicroorganism infection and sealed the fate of the patient. In conclusion, combined treatment for Nocardia and mycobacteria co-infection, although rare, should be considered initially for an immunocompromised patient with an AFB smear-positive specimen.

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以陽性抗酸性染色血液塗片爲表現的分支枝桿菌及奴卡氏菌的合併菌血症：一病例報告

張祐綸　周建宏

在臺灣結核桿菌感染是常見的流行病，而抗酸性染色陽性標本是結核分枝桿菌感染的診斷參考之一。如果抗酸性染色血液塗片呈陽性，最先想到的第一個診斷通常是全身性結核分枝桿菌感染或分支桿菌菌血症。在這裡，我們報導了一例以血液陽性抗酸性染色塗片為表現的鳥分枝桿菌和奴卡氏菌合併菌血症，以彰顯陽性抗酸性染色鑑別診斷的重要性。*(胸腔醫學* ***2018; 33: 14-19)***

關鍵詞：分支桿菌，奴卡氏菌，重症肌無力症，菌血症

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Massive Hemoptysis due to Left Inferior Phrenic Artery-to-Left Pulmonary Artery Fistula in the Lingular Lobe of the Lung: A Case Report and Literature Review

Ching-Chieh Lin, Tsai-Wang Huang*, Kai-Hsiung Ko**, Wann-Cherng Perng***, Chih-Feng Giian***, Ying-Chieh Chen***

Massive hemoptysis is a pulmonary emergency requiring immediate management, such as bronchial angiographic embolization or surgical intervention. It occurs in various pulmonary diseases and typically derives from the bronchial arteries. We herein report a very rare case of a patient bleeding from a left inferior phrenic artery-to-pulmonary artery fistula, accompanied by focal bronchiectasis in the left lingular lobe of the lung. In this case, pulmonary angiography was useful for clarifying the etiology and the abnormal anastomosis. In cases of hemoptysis with an uncommon etiology, video-assisted thoracic surgery with surgical resection of the bleeding vessel is the definitive management. ***(Thorac Med 2018; 33: 20-26)***

Key words: bronchiectasis, fistula, hemoptysis, non-bronchial artery

Introduction

Massive hemoptysis is defined as expectorated blood in excess of 200 mL within 24 h, and is life-threatening because of concomitant hypotension, airway obstruction, or blood loss. It is a pulmonary emergency caused by various underlying conditions [1], typically lung malignancies and chronic inflammatory conditions (including tuberculosis, bronchiectasis, and lung abscess) [2].

Non-bronchial systemic arteries have been identified recently as a crucial origin of bleeding in cases with massive hemoptysis. The progressiveness of the clinical presentation and the unpredictable development of life-threatening hemoptysis demand intensive evaluation and management. We herein report a rare case of

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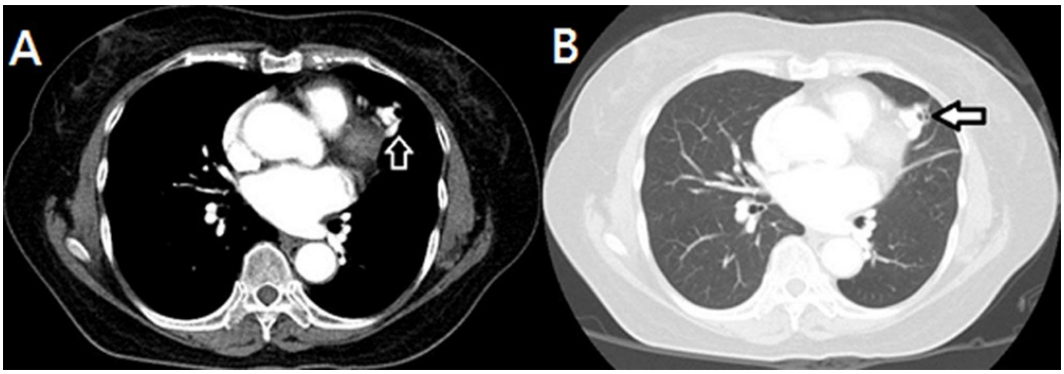

Fig. 1. Chest Contrast-Enhanced Computed Tomography. A hypervascular lesion (arrow) in the left lingular lobe, abutting the pericardial region (A). Focal bronchiectasis (arrow) in the left lingular lobe (B).

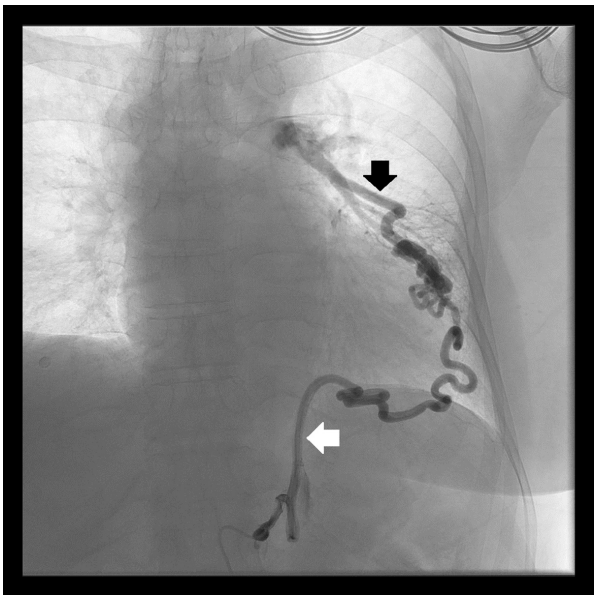

Fig. 2. Angiography. An engorged vascular anastomosis observed between the inferior branch of the left pulmonary artery (black arrow) and the left inferior phrenic artery (white arrow).

massive hemoptysis in a patient with focal bronchiectasis and left inferior phrenic artery (IPA)-to-pulmonary artery fistula. Bleeding was terminated through a surgical approach.

Case Report

The patient was a 71-year-old non-smoking woman who had a medical history of old pulmonary tuberculosis and bronchiectasis. She had symptoms of non-productive cough lasting 1 month and hemoptysis on the day before admission. The initial amount of expectorated blood was 2 bowlfuls. After treatment with a hemostatic agent, the patient expectorated 80 mL of bright-red blood within 6 h. No coagulopathy or thrombocytopenia was detected.

Physical examination revealed mild bilateral crackles. She was not febrile or hypoxic. Chest radiograph revealed left lower lobe infiltrates. Chest contrast-enhanced computed tomography (CT) showed a 2.4-cm serpentine hypervascular lesion in the left lingular lobe abutting the pericardial region (Figure 1A), with focal bronchiectasis in the left lingular lobe (Figure 1B). Arteriographic embolization was performed due to the initial impression of bronchiectasis with left IPA feeding, which we suspected to be the possible source of the massive hemoptysis. However, angiography disclosed an artery-to-artery fistula at the left lingular lobe, abutting the pericardial region, in which the left IPA communicated with the inferior branch of the left pulmonary artery (Figure 2). The finding of vascular anastomosis

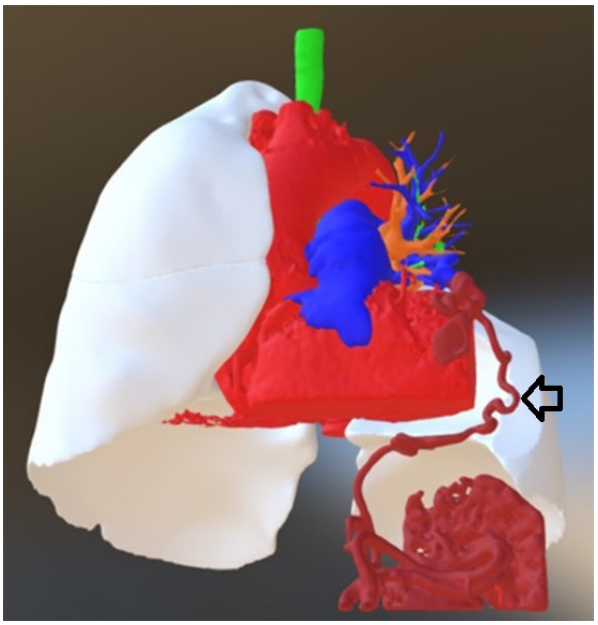

Fig. 3. Three-Dimensional Reconstruction Imaging. The feeding artery (arrow) arising from the subdiaphragm, located on the surface of the pericardium and supplying the left lingular lobe.

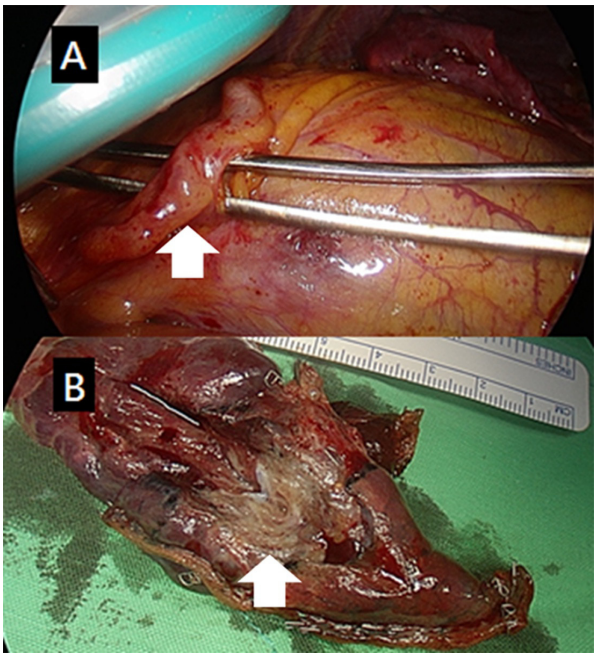

Fig. 4. Intraoperative Photograph. The feeding artery (arrow) arising from the subdiaphragm, via the pericardium, and supplying the lingular lobe of the lung (A). Bronchiectasis (arrow) with chronic inflammation of the lingular lobe was noted (B).

was also found on 3-dimensional reconstruction imaging (Figure 3). Due to the high flow of the pulmonary artery and the tortuosity of the IPA, we aborted the above therapeutic procedure.

We decided subsequently to perform video-assisted thoracoscopic surgery (VATS) with segmentectomy of the lingular lobe to prevent ongoing massive hemoptysis. The main supply artery arose from the left IPA and progressed to the lingular lobe of the lung (Figure 4A), and bronchiectasis (Figure 4B) was observed during VATS. After ligation of the supply artery, the patient gradually recovered, with progressive improvement of hemoptysis. She was discharged after 14 days in the hospital.

Discussion

The present case report describes an elderly woman who had a left IPA-to-pulmonary artery fistula with focal bronchiectasis, resulting in life-threatening hemoptysis. This condition is a respiratory emergency with a mortality rate of about 80% in the absence of further appropriate management [3-4]. It is important to confirm that lung vessels are the source of bleeding, and this involves excluding bleeding from vessels of the gastrointestinal tract or nasopharynx. The volume of bleeding usually correlates with patient outcome and duration of hospital stay. While patients with mild hemoptysis have a shorter hospitalization and usually have a better prognosis, patients with massive hemoptysis need a longer hospital stay and more surgical intervention [5]. The major causes of hemoptysis include bronchiectasis, bronchitis, pneumonia, and lung cancer. In a series reported in 1997, bronchiectasis accounted for 20% of

cases of hemoptysis [5]. In another study, bronchiectasis accounted for about 35% of cases with life-threatening hemoptysis [2].

The bronchial artery, from the systemic circulation, accounts for about 90% of bleeding sources in massive hemoptysis, and the pulmonary artery, from the pulmonary circulation, accounts for the remainder [6]. However, the non-bronchial systemic circulation may be involved in 10-30% of life-threatening hemoptysis cases [7-8]. Missing the non-bronchial systemic arteries in the angiography examination may result in recurrent bleeding. Many experts have suggested that a comprehensive examination of arteries involved in non-bronchial systemic supply should be performed in hemoptysis cases [9]. Also, some systemic arteries may induce hemoptysis, including the internal mammary, intercostal, and thyrocervical arteries, and the IPA. The IPA arises mainly from the celiac artery or aorta, and is well known as a provider of extrahepatic blood supply for hepatocellular carcinomas [6]. In many published cases of hemoptysis of IPA origin, the lower lobe of the lung was impacted with chronic inflammation and was apparently the source of bleeding [10-13]. Transpleural systemic-pulmonary artery anastomosis may occur in patients with tuberculosis, bronchiectasis, cystic fibrosis, or chronic pneumonia [10]. The possible mechanism underlying the development of this kind of transpleural systemic-pulmonary artery anastomosis is decreased pulmonary blood flow and pleural fibrosis. Some investigators have observed a tendency for a higher incidence of recurrent hemoptysis in patients with a systemic-pulmonary artery shunt [14-15]. In the present case, a left IPA-to-pulmonary artery fistula was the origin of bleeding in the lingular lobe, rather than in the lower lobe. The patient had focal bronchiectasis, and an abnormal systemic-to-pulmonary artery fistula developed due to chronic inflammation. Increased blood flow led to dilatation of the systemic arteries; thus, small vessels easily ruptured, with bleeding resulting from systemic pressure.

Pulmonary sequestration is a congenital disorder characterized by focal areas of anomalous lung tissue that lack normal communication with the tracheobronchial tree, and receive systemic arterial supply. In our case, there was non-bronchial systemic arterial circulation in the left lingular lobe. Therefore, pulmonary sequestration should be included in the differential diagnosis for the patient. However, chest contrast-enhanced CT and angiography of our patient clearly revealed focal bronchiectasis adjacent to an artery-to-artery fistula in the left lingular lobe. Clearly, there was normal communication with the tracheobronchial system in the present case. Furthermore, the lesion in our case was located in the lingular lobe, but a majority of pulmonary sequestration has been located in the lower lobes (96%) [16]. Based on the above findings, pulmonary sequestration could be excluded from the differential diagnosis of our patient.

Resuscitation and protection of the airway are the initial approaches to managing life-threatening hemoptysis. The next step is directed at localizing the source and cause of bleeding, and the final step includes intervention using definitive treatments to prevent recurrent bleeding. Bronchoscopy and angiography are the examinations of choice to confirm the site of bleeding and to perform therapeutic intervention. Bronchial artery embolization (BAE) is performed extensively for the treatment of hemoptysis, especially in severe, non-surgical cases. However, other sources of non-bronchial

systemic arterial supply and the IPA are accordingly assumed to diminish the therapeutic outcome of embolization. Furthermore, technical failure of BAE occurs in approximately 13% of cases, and is commonly caused by non-bronchial arterial supply from systemic vessels, such as the mammary, phrenic, intercostal, or subclavian arteries [17]. Complications of BAE include systemic embolization, vessel perforation, intimal tears, hemoptysis, pyrexia, and neurological complications. Surgery is effective for the management of localized lesions related to hemoptysis. Surgical resection is considered when BAE is unavailable, or if it is unlikely that the bleeding can be controlled by embolization. Surgical resection remains the management of choice for the treatment of life-threatening hemoptysis caused by particular cases of hydatid cyst, arteriovenous malformations, leaking aortic aneurysms, bronchial adenoma, iatrogenic pulmonary rupture, or hemoptysis associated with mycetoma, which are resistant to other means of management [18]. Compared to other therapies, surgical resection of the bleeding vessel is considered the definitive treatment. Furthermore, hemoptysis is usually complicated with respiratory distress, which can lead to desaturation after respiratory failure.

In our case, there were 2 reasons for the failure of BAE. First, the lumen of the artery-to-artery fistula was too large, which led to a very high flow rate. As a consequence, a steel coil could not be fixed to the precise site of the feeding vessel. Second, the IPA of our patient was too tortuous, and the coaxial microcatheter could not be extended to the distal part of the IPA. For patients with life-threatening hemoptysis for which BAE is ineffective, immediate surgery can be used to prevent the development of respiratory failure and the progression of bleeding.

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左肺舌葉之左下橫膈動脈到左肺動脈廔管合併大量咳血：病例報告與文獻回顧

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大量咳血是一種肺部急症，需要立即進行支氣管血管造影栓塞或外科手術。它發生於各種的肺部疾病，通常起源於支氣管動脈。我們的案例報告是一個 71 歲女性，曾有肺結核和支氣管擴張症的病史，最近 1 個月陸續有咳嗽症狀，入院前 1 天開始出現大量咳血，胸部電腦斷層發現左側肺部舌葉有異常的血管顯影合併支氣管擴張症。肺血管造影證實為一左下橫膈動脈到左肺動脈之廔管。最後，藉由胸腔內視鏡輔助手術切除異常部分的肺葉，並改善咳血的症狀。*(胸腔醫學* ***2018; 33: 20-26)***

關鍵詞：支氣管擴張症，廔管，咳血，非支氣管動脈

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Spinal Cord Infarction after Embolization of the Bronchial Artery due to Massive Hemoptysis: A Case Report and Literature Review

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Massive hemoptysis may be associated with high morbidity and mortality and may require emergency bronchial artery embolization (BAE). Complications following BAE for hemoptysis are rare. We report the case of an 87-year-old man with bronchiectasis who experienced cough with blood-streaked sputum for 3 days and hemoptysis for 1 day. With conservative treatment, the hemoptysis and dyspnea progressed. Angiography and BAE were performed. After the procedure, a sudden onset of right lower limb monoplegia occurred. Magnetic resonance imaging of the thoracic spine detected acute ischemic infarctions with water diffusion restriction at the ventral cord and right portion of the thoracic spinal cord (T3-T7 level). Treatment with an anti-platelet agent and a rehabilitation program were initiated. The right lower limb monoplegia improved gradually 3 months later. Embolization of the bronchial artery may have caused spinal cord infarction due to vascular occlusion. Early identification of this rare complication may be beneficial for successful treatment. ***(Thorac Med 2018; 33: 27-36)***

Key words: embolization, bronchial artery, spinal cord infarction

Introduction

Hemoptysis is among the most common symptoms in patients with respiratory diseases, and massive hemoptysis is a life-threatening condition in 5-15% of cases [1]. Furthermore, its mortality rate is more than 50% if not treated appropriately [2]. Patients with new-onset hemoptysis require thorough diagnostic evaluations that include computed tomography (CT) of the thorax and bronchoscopy. The cause of hemoptysis cannot be determined currently in 20-30% of cases [3]. The development of multidetector CT angiography may help in identifying the bleeding site.

In all, 90% of hemoptysis cases originate

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in the bronchial artery, 5% from the pulmonary circulation, and the remaining 5% from the non-bronchial systemic circulation [4]. Control of hemoptysis has been achieved through surgical intervention if conservative management fails. In past decades, bronchial artery embolization (BAE) was established as an emergency management procedure for not only massive hemoptysis but also chronic or recurrent hemoptysis that impairs the patient's quality of life [5-6]. Different materials are used for bronchial embolization, including polyvinyl alcohol (PVA) particles, PVA hydrogel, micro-coils, and gelatin sponge (gel foam) [7].

The first report of the use of BAE to control hemoptysis was published in 1974 [8]. Bronchial arteries larger than 2 to 2.5 mm in diameter usually are considered enlarged [9]. Angiographic findings indicating embolization of the affected vessel include the following: hypervascularity, tortuous and enlarged bronchial arteries, shunting into the pulmonary artery or vein, parenchymal staining, vascular abnormalities such as aneurysms, and extravasation into the airway [10-11]. Common complications of BAE include chest pain (24-91%) and dysphagia (0.7-18.2%), which can occur 2 to 7 days after embolization [12]. These symptoms, which are usually transient and regressive, are probably related to occlusion of intercostal and esophageal vessels. Sub-intimal dissection of the aorta or bronchial artery can also occur, but is frequently asymptomatic. Pulmonary infarction can complicate bronchial embolization when the bronchial artery is the only source of vascular supply to the lung, as in the case of chronic proximal pulmonary artery occlusion [13].

Spinal cord infarction is usually marked by acute onset of back pain and is associated with limb weakness, paresthesia, and sensory loss. Loss of sphincter control with hesitancy and the inability to void or defecate may also be involved [14]. The severity of the condition depends on the level of the infarcted spinal cord lesion and varies, with mild to moderate neurologic sequelae and even reversible leg weakness to quadriplegia. The initial neurologic assessment has proven to be the predictor of the prognosis and outcome [15]. Spinal cord infarction after BAE is seldom reported in the literature. However, it may be the most devastating adverse effect. Herein, we present a case of massive hemoptysis after BAE that was complicated with ischemic infarction of the spinal cord.

Case Report

An 87-year-old man with a cigarette smoking history of 1 pack/year for 50 years presented with symptoms of chest tightness, shortness of breath, and productive cough with a moderate amount of blood-streaked sputum for 3 days and hemoptysis for 1 day. Chest radiograph revealed fibro-calcified opacities in the right upper lung with increased interstitial marking and ground-glass opacities of both lungs. Laboratory tests indicated the following: white blood count of 8,520 (normal range, 4,500-11,000/μl); hemoglobin level of 14.3 g/dl (normal range for men, 13.5-18.0 g/dl); platelet count of 167,000/μl (normal range, 150,000-400,000/μl); prothrombin time of 10.4 sec (normal range, 8.0-12.0 sec); activated partial thromboplastin time of 32.1 sec (normal range, 23.9-35.5 sec); and C-reactive protein level of 1.46 ng/ml (normal range, <0.8 mg/dl). Nasopharyngoscopy and panendoscopy showed no abnormal findings. Multi-detector CT revealed fibro-nodular opaci-

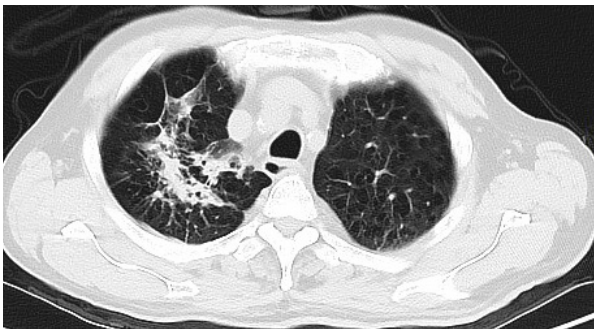

Fig. 1. Chest computed tomography revealed traction bronchiectasis combined with adjacent lung consolidation and ground-glass opacity, indicating the site of hemoptysis.

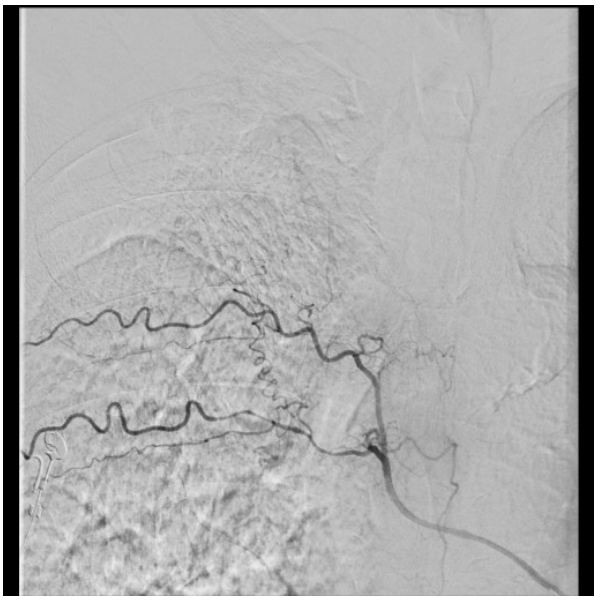

Fig. 2. Bronchial angiography detected bronchial artery hypervascularity in the right upper lobe, corresponding to the bronchiectasis noted on chest computed tomography.

ties with traction bronchiectasis in the right upper lobe and diffuse emphysema of both lungs (Figure 1). Bronchoscopy showed massive blood clot retention at the trachea and right main bronchus, but no active bleeding site was seen. Bronchial washing examination revealed negative results for acid-fast bacilli. Hemoptysis secondary to bronchiectasis with secondary infection was diagnosed. Hemostatic agents, antibiotics with levofloxacin and antitussive agents were administered initially as conservative management. Minor hemoptysis remained with conservative treatment.

Two days later, massive hemoptysis with a blood loss of about 150-200 ml and dyspnea were found. Then, another hemoptysis episode with about 100 ml of blood loss occurred a half hour later. Emergency angiography was performed, but did not show communicating anastomosis between the bronchial artery and the spinal artery, or anterior medullary artery, which usually has a characteristic hairpin-loops appearance overlying the vertebral column. A catheter was introduced into the descending thoracic aorta, using a right superficial femoral artery approach, and reached the right superior bronchial artery. Tortuous neovascular vessels with contrast stasis in the corresponding area of the right upper lobe of the lung were seen (Figure 2). Therapeutic BAE was performed using absorbable gel foam pieces as the embolic material. Sluggish flow at the proximal segment of the right superior bronchial artery was seen on post-embolization angiography (Figure 3).

Six hours after this procedure, the patient reported severe back pain and right lower limb weakness and numbness. There was no incontinence. Physical examination of the right lower limb showed markedly decreased muscle power (grade 0/5) with an absent Babinski sign. Deep tendon reflexes were diminished at the right knee. Impaired sensory function below the T10 dermatome was also found. The anal tone was normal. Brain CT disclosed no evidence of acute cerebral hemorrhage or ischemia. Vessel Doppler sonography showed good blood flow to the lower extremities. Thoracic spine magnetic resonance imaging was performed and showed

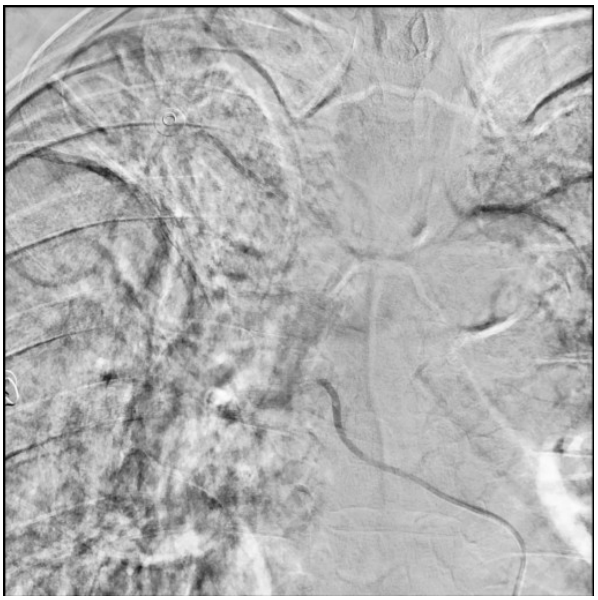

Fig. 3. Post-embolization angiography revealed nearly complete stasis of flow at the lateral branch of the right superior bronchial artery.

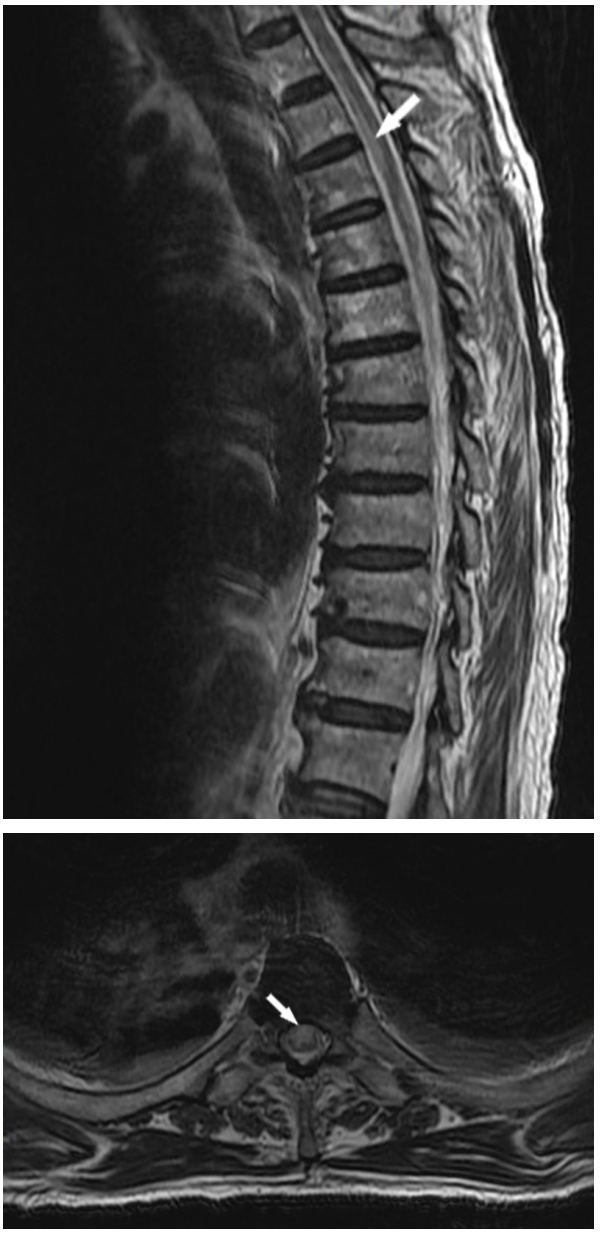

Fig. 4A, 4B. Thoracic spine MRI T2-weighted images showing acute ischemic infarctions with hyperintensity signal at the ventral cord and right portion of the cord (T3-T7 level; arrow), sparing the dorsal cord.

acute ischemic infarctions with water diffusion restriction at the ventral cord and right portion of the thoracic spinal cord (T3-T7 level) (Figure 4A, 4B). Acute thoracic spinal cord infarction was diagnosed.

Hemoptysis subsided after BAE. The patient was managed with an anti-platelet agent with cilostazol (100 mg/day for 28 days), and rehabilitation program for spinal cord infarction with right lower limb monoplegia. Three months later, numbness of the right lower limb subsided, and gradually improved muscle power of the right lower limb (grade 3/5) was noted.

Discussion

We presented a rare case of spinal cord infarction related to right lower limb monoplegia after gel foam embolization of the bronchial artery for massive hemoptysis. Massive hemoptysis is defined as blood loss exceeding 200 to 600 ml within a period of 24 hours or less [31]; it is a medical emergency since the reported mortality rate can be as high as 75%. In addition to the present case, we identified 10 patients with spinal cord infarction after BAE dur-

ing a Medline search of the literature (Tables 1 and 2) [11,18-19,25-28]. Seven of these patients were reported in 4 case series. The incidence of spinal cord infarction after BAE ranged from 1.4% to 6.3%. Three other patients were found in case reports.

In general, the left bronchial arteries originate from the aorta, and the right bronchial arteries originate from an intercostobronchial trunk. Vascular distribution of the bronchial arteries includes mediastinal structures, pleura, bronchi, the esophagus, and the walls of the thoracic and pulmonary vasculature [16]. The spinal cord is supplied by 3 longitudinal arteries: the single anterior spinal artery supplies the anterior two-thirds of the spinal cord; the paired posterior spinal arteries supply the posterior one-third of the spinal cord; and anastomoses between the spinal arteries (called the arterial vasocorona) supply the peripheral lateral aspect of the spinal cord. These arteries originate at or near the cervico-occipital junction, but they are small-caliber and discontinuous. Therefore, they require reinforcement by segmented arteries, which divide into radicular and medullary arteries [17]. Damage to the dominant segmented artery, which can have variable origins, may cause spinal cord infarction. Bronchial and intercostal arteries emit dorsal and ventral radicular arteries that supply the dorsal and ventral nerve roots. Anterior medullary arteries also arise from the bronchial and intercostal arteries and communicate with the anterior spinal artery to supply the spinal cord. Because of the complicated anastomosis between the bronchial circulation and the spinal arteries, embolization of bronchial arteries may cause an inadvertent embolic event in the radicular medullary arteries, which results in spinal cord ischemic infarction [19].

The advantages and disadvantages of the use of embolic materials for BAE are evaluated based on multi-dimensional scaling, including rapidity, completeness of vessel occlusion, control of embolization material spreading into the vessel, and the time window for the procedure [20]. To prevent non-target damage to small normal collateral arteries, and the risk of aortic, esophageal, bronchial, or pulmonary artery wall necrosis, smaller particles or liquid embolic agents should be avoided. Coils should also be avoided to preserve access to future sites of bronchial bleeding and to allow retreatment of an affected vessel [21]. The most widely used embolic agents are PVA particles and gelatin sponge (gel foam). PVA particles are preferred to gel foam because gel foam is resorbable and may not provide a result that is as durable as that provided by permanent agents such as PVA [22]. In the literature review, we found little information about the relationship between the embolic agent used and spinal cord infarction after BAE. However, 3 patients who received gel foam experienced improved neurologic symptoms [19,25,28]. With our patient, gel foam was used as the embolic material for BAE. Partial recovery of neurologic sequelae was seen after spinal cord infarction, which might imply that gel foam provides a better outcome when encountering embolization-related ischemia, due to its resorbability.

In the literature review, it seemed that no matter which culprit vessel was selected for embolization, the possibility of spinal cord infarction after BAE remained. Careful analysis of the angiogram before and during the embolization procedure is crucial for prevention of this complication. A thorough knowledge of normal and variant bronchial artery anatomy, as well as collateral supply, is necessary before em-

Table 1. Literature Review of Spinal Cord Infarction after Bronchial Artery Embolization

Reference	Mean age, years (range)	Gender (male/ female)	BAE site	Embolization material	Symptom	Treatment	Prognosis
Ramakantan *et al*. [11]	31.5	125/15	Not mentioned	Gelatin sponge (gel foam)	Transient paraparesis (n=2, 1.4%)	Not mentioned	Not mentioned
Tanaka *et al*. [25]	57.9 (27-86)	30/17	Right bronchial artery (35.84%); left bronchial artery (33.96%); common bronchial trunk (9.43%); intercostal artery (9.43%); subclavian branch artery (11.32%)	Gelatin sponge (gel foam)	Sensory and motor loss (n=1, 2.1%)	Rehabilitation	Without sequelae
Mal *et al*. [26]	51 (19-89)	30/16	Not mentioned	Gelatin sponge (gel foam); tris-acryl microspheres; dura mater; polyvinyl alcohol; bucrylate	Episodes of neurologic damage (n=3, 6.3%)	Not mentioned	Without sequelae (n=2); complete paraplegia without regression (n=1)
Wong *et al*. [27]	49 (27-72)	13/ 3	Left bronchial artery (n=5); right bronchial artery (n=7); left intercostobronchial artery (n=1); right and left common bronchial trunk artery (n=2); right and left bronchial artery (n=1)	Polyvinyl alcohol	Transient paraparesis (n=1, 6.3%)	Not mentioned	Without sequelae

barking on an embolization procedure. Prior to BAE, the number and origin of bronchial arteries from the aorta or intercostobronchial trunk should be carefully evaluated to determine the optimal angiographic approach.

In our presented case, angiography did not show a hairpin-loops configuration, indicating that anterior medullary arteries were not seen. The radicular artery is often visualized during BAE, but unintentional embolization of the radicular artery usually does not cause clinical problems like spinal cord ischemia [9,21]. The incidence of neurogenic compromise has not been reported with inadvertent radicular

Table 2. Case Reports of Spinal Cord Infarction after Bronchial Artery Embolization

Reference	Age, years	Sex	BAE site	Embolization material	Symptom	Treatment	Prognosis
Brown *et al*. [18]	70	Male	Right 7th intercostal artery	Polyvinyl alcohol	Bilateral legs weakness and skin temperature change	Rehabilitation	Partially recovered
Maramattom *et al*. [19]	65	Male	Left bronchial artery	Gelatin sponge (gel foam)	Left leg weakness, paresthesia and urinary retention	Intravenous methylprednisolone (1 g/day × 5 days)	Muscle power improved (grade 0/5 to 4/5)
Jammoul *et al*. [28]	44	Female	Left bronchial artery	Gelatin sponge (gel foam)	Left leg weakness, numbness, and urinary hesitancy	Not mentioned	Completely recovered
Present case	87	Male	Right superior bronchial artery	Gelatin sponge (gel foam)	Right leg monoplegia	Rehabilitation and oral anti-platelet agent	Muscle power improved (grade 0/5 to 3/5)

artery embolization, but embolization should be avoided when the anterior medullary artery is observed on angiography, because it is the major independent source of spinal artery perfusion, and accidental spinal cord ischemia may occur with BAE [21].

This case indicates that angiographically invisible small vessels can play an important role in supplying blood to the spinal cord. Hypertrophied, tortuous bronchial arteries or collateral vessels, and diffuse atherosclerosis of blood vessels in elderly patients may lead to unsafe embolization due to compromised blood flow to the spinal cord [32], and may cause difficulty in the precise placement of embolic agents in the target vessel. Furthermore, reflux of embolic material backward into normal circulation may occur, and cause unintentional occlusion that impedes the normal spinal cord blood supply [23,32]. Besides, embolization of a bronchial artery at a proximal location may result in inadvertent occlusion of nearby blood vessel branches related to the spinal cord. The safety of BAE also depends on the radiologist's experience and technique. All of the above-mentioned conditions may be considered as contributing factors in this case. The usefulness of a micro-catheter for selective BAE has been emphasized in many recent articles [23-24]. This very selective catheterization permits stabilization of the catheter position within the bronchial artery and safe positioning in the bronchial circulation, bypasses the origin of the spinal cord branches, and prevents reflux of embolic agents into other non-target regions.

Poor prognostic factors for recovery from spinal cord infarction due to other diseases include severe impairment at presentation, female sex, advanced age, and lack of improvement during the first 24 hours [29-30]. In the literature review, there was no consensus regarding standard treatment for BAE-related spinal cord infarction. Systemic steroids were used in 1 case report [19], and, with adequate rehabilitation, 2 patients experienced improvements in neurologic sequelae [18,25].

In conclusion, embolization of the bronchial artery may cause spinal cord infarction due to vascular occlusion. Proper identification of the culprit bronchial vessel and its anastomosis can minimize the chances of this complication. Early identification of this rare complication may be beneficial for successful treatment.

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咳血經支氣管動脈栓塞術後併發脊柱缺血性梗塞：病例報告與文獻回顧

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大量咳血病患會有較高的相關併發症及死亡率，需要緊急執行支氣管動脈栓塞術。咳血經支氣管動脈栓塞術後之併發症極少見。本案例是一個 87 歲男性，有支氣管擴張症病史，最近 3 天開始出現咳嗽帶血痰，以及咳血情形 1 天。支氣管鏡檢查顯示在氣管及右側支氣管有血塊，但是沒有發現自發性出血點。經住院保守治療後，仍然持續有大量咳血及呼吸急促情況，因此執行血管攝影及支氣管動脈栓塞術。術後突發右下肢偏癱情形 , 經胸椎核磁共振檢查，確診是胸段脊柱急性缺血性梗塞 (T3~T7 高度；腹側及右側區域脊柱)。經給予抗血小板藥物治療與復健，右下肢偏癱情形在三個月後逐漸改善。支氣管動脈栓塞術可能會導致脊柱缺血性梗塞。確認此少見的併發症，有助幫助早期診斷及成功的治療病患。*(胸腔醫學 **2018; 33: 27-36**)*

關鍵詞：栓塞術，支氣管動脈，脊柱缺血性梗塞

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Eyelid Metastasis from Adenocarcinoma Lung Cancer – A Rare Case Report

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Eyelid metastases are rare, representing less than 1% of malignant eyelid lesions. Eyelid metastasis usually presents with a variety of clinical features. Symptoms of lung cancer often do not present until the advanced stages. We report a very rare eyelid tumor finally confirmed to be metastasis from lung adenocarcinoma. A 64-year-old woman had a 3-month history of flesh-colored bumps on the right lower eyelid and left nasocheek. Biopsy and immunohistochemical evaluations of the eyelid lesion and nasocheek skin lesion confirmed the diagnosis of lung cancer with eyelid metastasis. In this case report, we highlight the importance of a more detailed workup, including biopsy, IHC study, and gene analysis, to determine the exact nature of an eyelid lesion. ***(Thorac Med 2018; 33: 37-42)***

Key words: eyelid metastasis, eyelid lesion, lung carcinoma

Introduction

Primary eyelid cancer is a rather common eyelid tumor in adults; however, metastatic eyelid disease is rare, and accounted for less than 1% of all malignant eyelid tumors in a literature review [1]. The most common malignancies that will metastasize to the eyelid are breast cancer [2-3], prostate cancer [3], skin or uveal melanoma [1,3], renal cell carcinoma [4] and neuroendocrine carcinoma [5]. The association of eyelid metastasis with lung adenocarcinoma has rarely been reported; here, we report a rare case of lung cancer presenting with eyelid metastasis, including the genetic associations, immunostaining characteristics, and treatment.

Case Presentation

A 64-year-old woman initially presented to the dermatology department clinic with a 3-month history of flesh-colored bumps on the right lower eyelid and left nasocheek. She denied any systemic disease or any remarkable ophthalmic history. She had been referred to our dermatology clinic and received laser treatment twice, but without success. An excisional biopsy was performed. Two pieces of skin measur-

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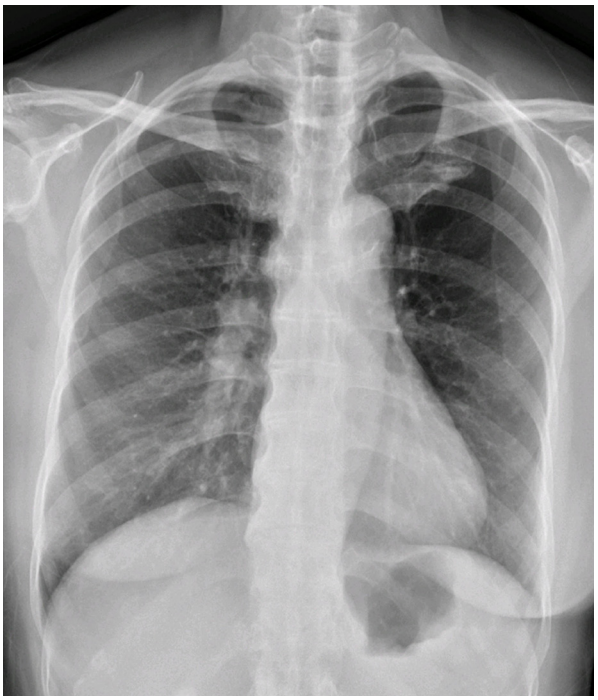

Fig. 1. Chest radiography showing more linear densities in the lung field.

ing up to 0.4×0.3×0.1 cm in size were analyzed. The pathology report showed pictures of dermal metastatic adenocarcinoma featuring round nuclei and moderate cytoplasm arranged in an irregular glandular or acinar pattern. Lymphatic permeation was also noted. Histopathologic examination revealed immunoreactivity to TTF-1 and CK7, but was negative for CK20 and GATA3 (Figure 3). Therefore, thyroid cancer or lung cancer was considered to be the primary origin. Physical examination also revealed mild enlargement of the neck. The patient underwent thyroid ultrasound, which showed multiple tiny nodules with cystic content, microcalcification and eggshell calcification.

Thyroid biopsy was performed and papillary neoplastic cells and neutrophils were reported. Laboratory test results showed a thyroglobulin Ab level <20 IU/mL (reference range <40 IU/mL), microsomal Ab level <10 IU/mL (reference range <35 IU/mL), thyroglobulin level 2.70 ng/mL (reference range <50 ng/mL), free T4 level 0.91 ng/dL (reference range 0.7-1.8 ng/dL), T3 level 73.20 ng/dL (reference range 60-190 ng/dL), TSH level 1.51 μIU/mL (reference range 0.25-4 μIU/mL), CEA level 43.67 ng/mL (reference range 0-5 ng/mL), SCC level 0.7 ng/mL (reference range 0-1.5 ng/mL), and TPA level 94.20 U/L (reference range <75 U/L). After serial survey, eyelid tissue was also analyzed. Since the immunohistochemical study of thyroglobulin was negative, thyroid cancer was not considered.

The chest x-ray revealed more linear densities at the lung field (Figure 1). Computed tomography (CT) scan of the chest showed a large soft tissue nodule at the right lower lobe with multiple small nodules in both lungs, mainly at the right lower lobe. Lymphadenopathies at the right supraclavicular region, right posterior cervical space, subcarinal region, and right hilar regions were found (Figure 2). Therefore, the patient also underwent right supraclavicular lymph node biopsy. The pathology report revealed metastatic adenocarcinoma, and the microscopic examination showed metastatic carcinoma cells, with eccentric nuclei and eosinophilic cytoplasm, forming clusters in fibroadipose tissue. MRI scan of the brain showed evidence of metastatic tumors with perifocal edema at bilateral cerebral hemispheres (with the largest at the left occipital lobe). A whole-body bone scan reported multiple bone metastases. Bronchoscopic biopsy was arranged for tissue proof, but failed due to unstable blood pressure. Analysis of the eyelid tumor showed an epithelial growth factor receptor (EGFR) mutation presenting with a deletion in exon 19. Afatinib 30 mg daily for lung adenocarci-

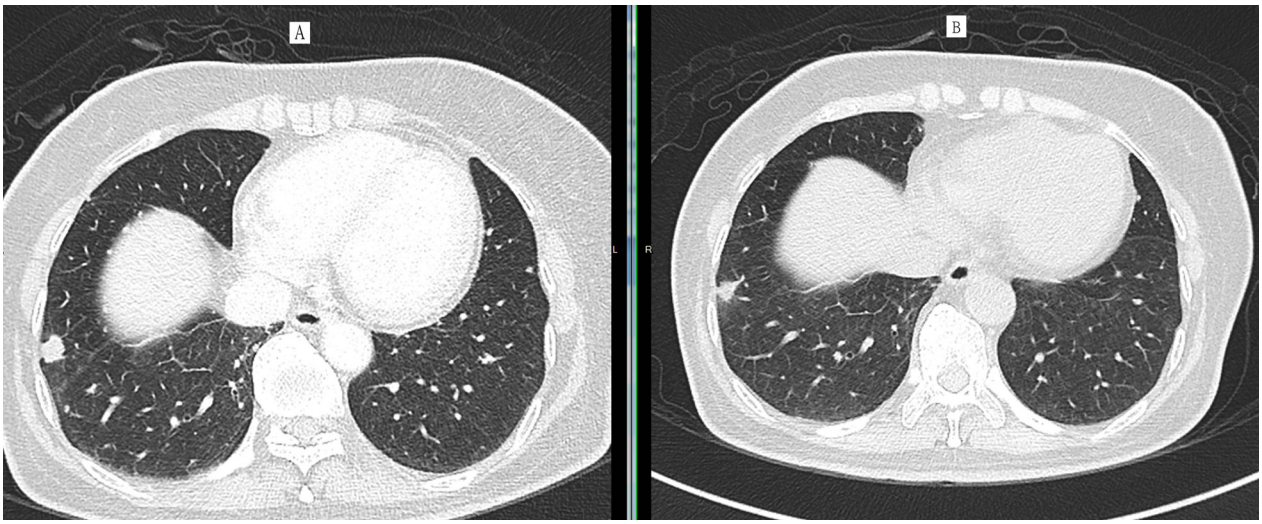

Fig. 2. (A) Before treatment, coronal sections of contrast-enhanced chest CT revealed a soft tissue nodule at the right lower lobe with multiple small nodules in both lungs. (B) Five months after treatment, CT scan of the chest showed a decrease in the size and number of metastases in both lungs.

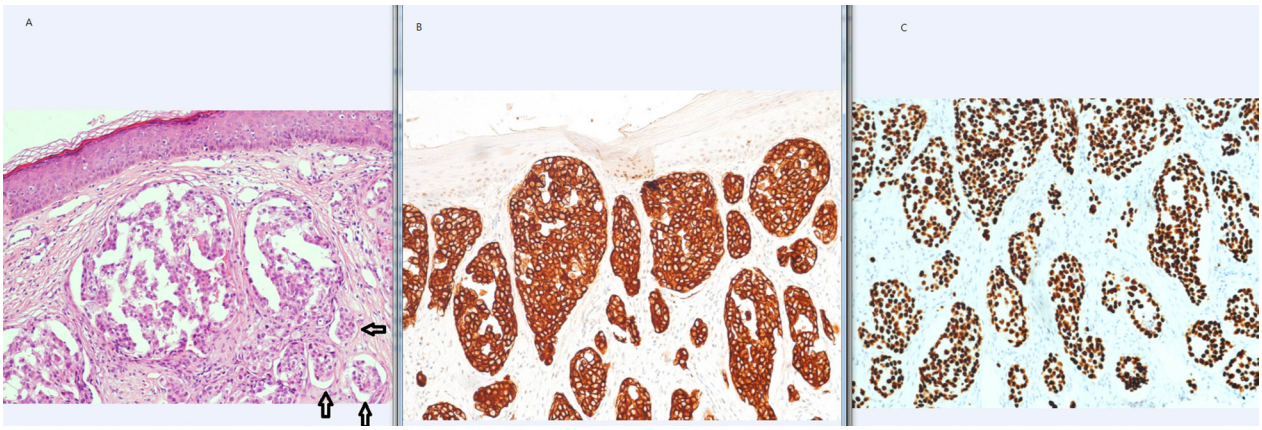

Fig. 3. (A) Hematoxylin & eosin staining (X100) section showed dermal metastatic adenocarcinoma featuring round nuclei and moderate cytoplasm arranged in an irregular glandular or acinar pattern. Lymphatic permeation was also noted (arrows). (B) Immunohistochemical staining of CK7 showed positivity in both cytoplasm and membrane. (C) Immunohistochemical staining of TTF-1 showed diffuse positivity in tumor cell nuclei.

noma was given, and Xgeva 120 mg SC per 4 weeks was prescribed for bone pain control. After 5 months, follow-up CT scan of the chest showed a decrease in the size and number of metastases in both lungs, and a decrease in the size and number of lymphadenopathies at the mediastinum and right hilar regions. At the time of writing this article, 6 months after her initial presentation, the patient was still being treated with afatinib 30 mg daily and Xgeva 120 mg SC per 4 weeks.

Discussion

The eyelid can be the site of both primary and metastatic cancers. Dekmezian *et al* published a review of cancers that can present on the eyelid, including their genetic associations and immunostaining characteristics. An eyelid lesion often requires biopsy for definitive diagnosis [1]. Metastases to the eyelids are rare, accounting for less than 1% of all malignant eyelid lesions. Breast carcinoma, skin melanoma, gastric carcinoma, uveal melanoma and lung carcinoma are the most commonly associated malignancies [3,6]. Eyelid metastases have been reported to present as a solitary eyelid nodule, a flat, pigmented lesion, diffuse eyelid edema and epiphora. Eyelid lesions can be an initial presentation of systemic malignancy. A high index of suspicion is needed for early diagnosis. Most information about eyelid metastases comes from individual case reports and a few small case series [7-12]. Primary lung cancer is common, but primary lung cancer with metastases to the eyelid is rare in Taiwan. This patient had no significant ophthalmic history and the initial examination was nonspecific. Therefore, biopsy of suspicious lesions is recommended.

It is now common for cancer patients to undergo genetic analysis of their tumors to test for driver mutations, which control the proliferation and survival of cancer cells. Lung cancers have been found to mutate somatically, and it is now a standard procedure to test EGFR mutations and ALK rearrangements in patients with metastatic lung adenocarcinoma, to determine further treatment [9]. Many studies have found that oral-targeting drugs have a better effect in patients with EGFR mutations. Asian populations with non-small cell lung cancer (NSCLC) with EGFR mutations have about a 40% chance of common mutations being located in exon 19 or exon 21 (L858R). This patient's lung tumor was positive for EGFR mutation with an exon 19 deletion, and it had metastasized to the brain and bone. Afatinib is currently indicated for treatment of patients with locally advanced or metastatic NSCLC with EGFR mutations as first-line therapy in Taiwan [13].

Conclusion

We reported a rare case of a middle-aged woman who presented with a right lower metastatic eyelid lesion arising from lung adenocarcinoma. EGFR mutation investigation reported the presence of a deletion in exon 19, and she accepted targeted therapy, which contributed to a better outcome.

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肺腺癌的眼瞼轉移－一個罕見病例報告

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癌症眼瞼轉移是罕見的，佔惡性眼瞼病變的百分之一以下，並且呈現多種臨床特徵。肺癌的症狀通常不顯著，且直到更晚期的階段才被發現。我們報告非常罕見的眼瞼腫塊，證實是肺腺癌的轉移。一個 64 歲的女性有一個三個月的病程，在右下眼瞼和左鼻孔臉頰處有一些肉色腫塊。眼瞼與鼻孔臉頰皮膚經組織切片檢查和免疫組織化學分析，顯示主要可能起源於甲狀腺癌或肺癌。這種情況之下，我們更強調詳細的檢查工作，包括組織切片檢查，確定病變的確切性質的重要性。*(胸腔醫學 **2018; 33: 37-42**)*

關鍵詞：眼瞼轉移，眼瞼病變，肺癌

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Radiocontrast-Induced Acute Respiratory Distress Syndrome (ARDS): A Case Report

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Hypersensitivity to radiocontrast media is not a common clinical event, and life-threatening delayed-type hypersensitivity is even less encountered. Herein, we present the case of a 57-year-old man with idiopathic pulmonary fibrosis, who underwent coronary angiography as part of pre-lung transplant evaluation. After angiography, the patient's oxygen demand substantially escalated over time, and non-cardiogenic lung edema developed. When considering the cause, hypersensitivity seemed more likely than infection. When the patient's clinical condition deteriorated, and even mechanical ventilation and pure oxygen failed to support the patient's respiratory needs, we summoned veno-venous extracorporeal membrane oxygenation to combat acute respiratory distress syndrome, and used steroids judiciously. The patient recovered gradually and was successfully bridged to lung transplant at post-contrast day 29, after this unexpected delayed-type hypersensitivity crisis was resolved. ***(Thorac Med 2018; 33: 43-49)***

Key words: radiocontrast media, acute respiratory distress syndrome, hypersensitivity

Introduction

With the development and progress of modern-day medicine, the increasing use of radiocontrast media (RCM) during radiologic examinations world-wide raises the issue of adverse events associated thereof. Among these adverse events, life-threatening delayed hypersensitivity is rare, and is most reasonably unanticipated and unwanted. In the case reported below, a high index of clinical suspicion and timely provision of extracorporeal membrane oxygenation (ECMO) and steroid treatment led to the full recovery of a lung transplant (LTx) candidate from delayed hypersensitivity crisis.

Case Report

A 57-year-old man, who had hypertension under medication control, presented to our hospital due to aggravated dyspnea during the past 2 years. He sought medical attention originally at a local hospital in August, 2013, where coronary angiography revealed coronary artery disease. The patient underwent percutaneous occlusive balloon angioplasty, and drug-eluting stents were inserted into the left anterior descending artery and left circumflex artery.

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At the same time, chest computed tomography (CT) showed bilateral pulmonary fibrosis. Further clinical workup did not disclose a definite pathology to account for the patient's lung fibrosis. Thus, under the impression of idiopathic pulmonary fibrosis (IPF), the patient received oral predonine treatment. Later, disease progression was noted, and the patient visited our hospital in March 2014 for LTx evaluation.

Upon admission, arterial blood gas analysis showed poor PaO_2 (45.0 mmHg) under room air, and IPF in progression was observed by follow-up chest CT. Transthoracic echocardiogram showed concentric left ventricular hypertrophy with left atrium dilation and pulmonary hypertension; the left ventricular ejection fraction was 59.4%. The pulmonary function test revealed a mild to moderate restrictive ventilatory defect, with forced vital capacity (FVC) of 1.91 L (60.2% of predicted value), and forced expiratory volume in 1 second (FEV_1) of 1.8 L (69.3% of predicted value). Severe impairment of diffusion capacity was also found, with a diffusing capacity of the lung for carbon monoxide of 5.83 ml/min/mmHg, which was only 23.9% of predicted value. Together, the clinical and laboratory findings pointed to a suspected diagnosis of IPF with cardiopulmonary distress. In order to re-evaluate the patency of the coronary artery and cardiac function, left cardiac catheterization was arranged. Coronary angiography with Ioversol contrast medium was performed, and showed no in-stent restenosis and fair cardiac output (5.2 L/min). The procedure was completed smoothly and without complications, and the patient was sent back to the general ward.

However, fever up to 38.2 degrees Celsius with marked dyspnea occurred a few hours after the angiography procedure (designated as post-contrast day 0), and the patient could barely maintain SpO_2 at 90-91% under nasal cannula. Chest roentgenogram did not show any marked abnormalities (Figure 1). Preliminary septic workup and empirical antibiotic were provided, as the patient remained febrile. The patient's oxygen need escalated dramatically, even requiring non-rebreathing mask. With oxygen supplied at a flow rate of 15 L/min, his respiratory rate was sustained at 30-35/min, and the SpO_2 hovered around 91-93%. With markedly increased oxygen demand and bilateral lung white-out, as demonstrated by chest roentgenogram (Figure 2), the patient was transferred to the surgical intensive care unit on the next day, post-contrast day 1. The patient was further intubated due to profound desaturation, in which the PaO_2/FiO_2 ratio was only 51.42 mmHg. Acute respiratory distress syndrome (ARDS) was established. The patient then underwent veno-venous (V-V) ECMO implantation on post-contrast day 2, due to acidemia (pH=7.109) and

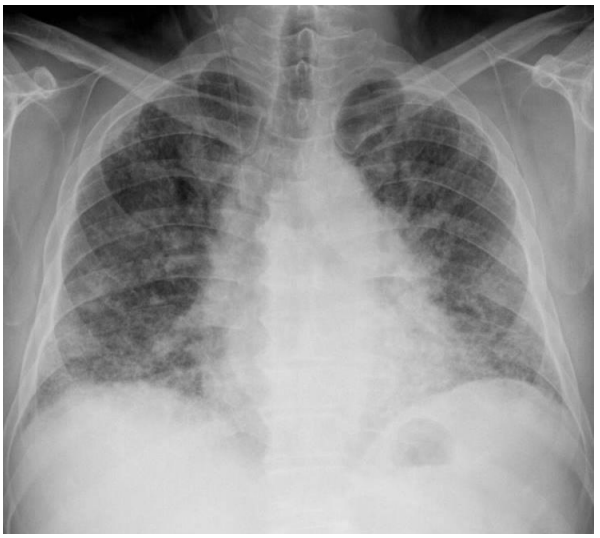

Fig. 1. Chest roentgenogram on post-contrast day 0: no significant abnomalities such as patches, consolidation, or atelectasis to account for the increased oxygen demand.

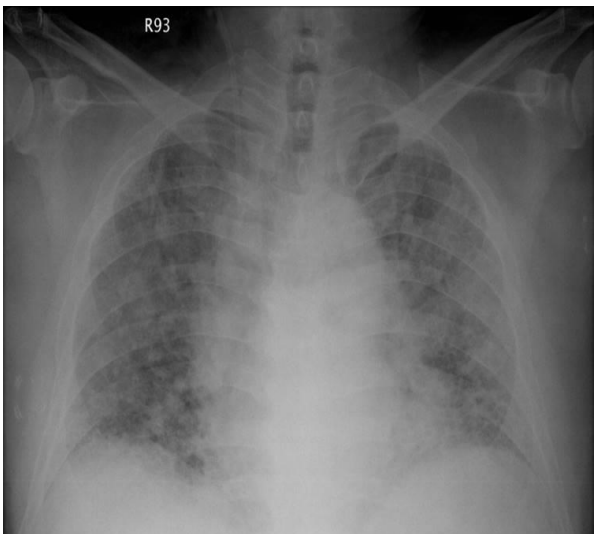

Fig. 2. Chest roentgenogram on post-contrast day 1: Initiation of bilateral lung infiltration.

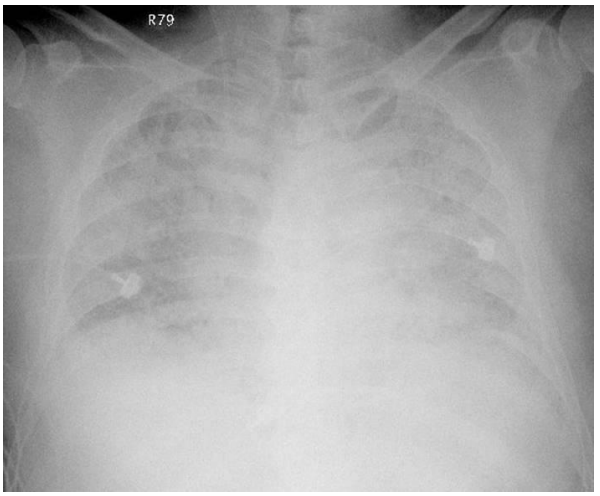

Fig. 3A. Chest roentgenogram on post-contrast day 2: Progression to marked bilateral lung white-out, which obscured the cardiac shadow and the diaphragm.

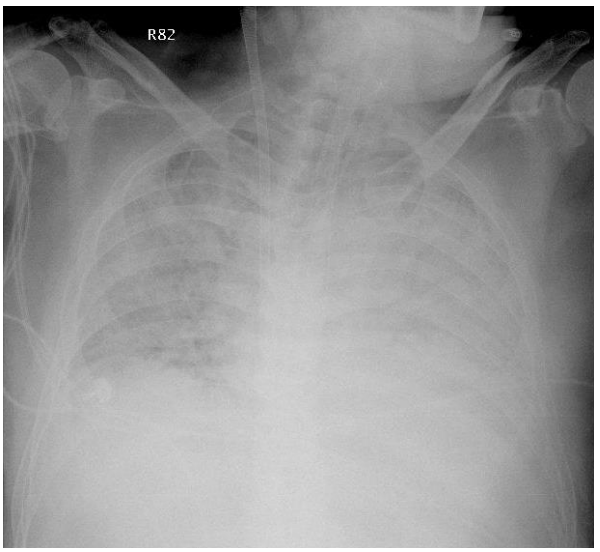

Fig. 3B. Chest roentgenogram on post-contrast day 2: Endotracheal intubation and V-V ECMO implantation were instituted.

CO_2 retention (pCO_2=148.5 mmHg), despite intubation with mechanical ventilation support (Figure 3, A-B). In addition to broad spectrum antibiotics, intravenous steroid was administered, also beginning on post-contrast day 2. All bacterial, fungal, and viral culture data were negative. Hence, given the causal relationship between coronary angiography and subsequent clinical events, and excluding the leading differential diagnosis, i.e., infection ─ delayed-type hypersensitivity, radiocontrast-induced, emerged as the probable alternative. During the following days, the patient's fever subsided, and his oxygen demand, arterial blood gas, and chest roentgenogram improved gradually (Figure 4, A-B). While antibiotic treatment continued, the steroid dosage was steadily tapered. On post-contrast day 7, V-V ECMO was successfully removed, due to the substantial recovery of the patient's clinical condition. The patient was extubated on post-contrast day 10. Soon, the patient was transferred to the general ward. He was discharged on post-contrast day 20.

Of note, the patient underwent successful bilateral sequential LTx from a cadaveric donor on post-contrast day 29.

Discussion

After serial survey, the patient was diagnosed with IPF. He underwent coronary angi-

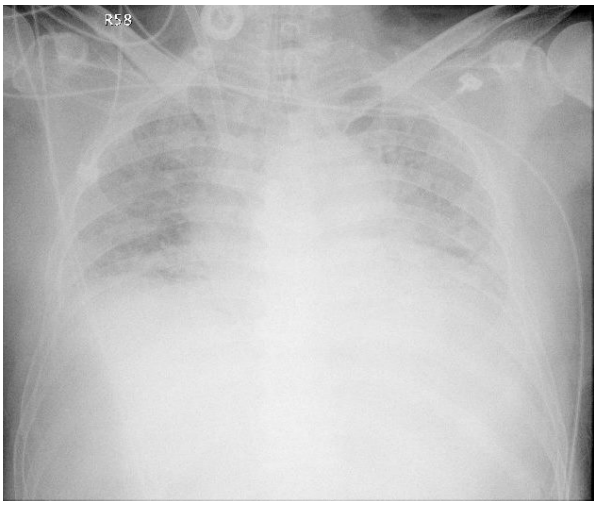

Fig. 4A. Chest roentgenogram on post-contrast day 6: Progressive clearing of lung fields.

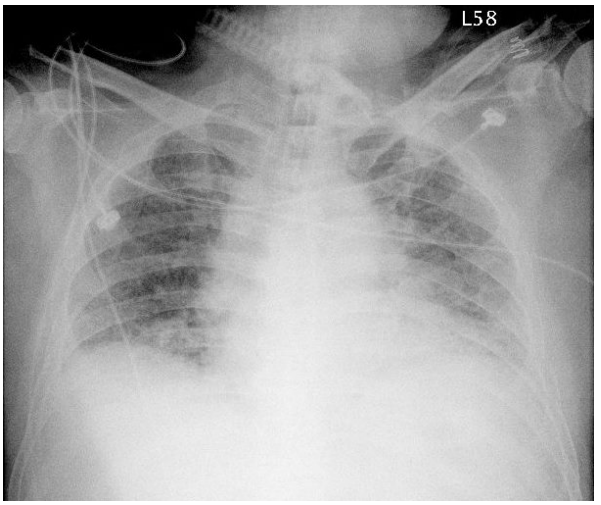

Fig. 4B. Chest roentgenogram on post-contrast day 8: V-V ECMO removal due to ARDS resolution.

ography twice: the first time, for assessment of cardiac function and ruling out cardiogenic causes; and 8 months later, for pre-LTx evaluation.

RCM administration was a necessity for the patient; however, its clinical sequelae were somewhat unexpected. The adverse events seen after contrast media administration may be divided into 3 different types: toxic reactions, allergic and non-allergic hypersensitivity reactions, and events unrelated to contrast media exposure [1]. Hypersensitivity reactions were further subclassified into immediate (≤1 hour) and non-immediate (>1 hour to 7 days) reactions [1-2]. Urticaria, pruritus, and angioedema, and more infrequently, nausea, dyspnea due to bronchospasm, and hypotension, are the major clinical manifestations of immediate hypersensitivity to RCM [2-3]. On the other hand, dermatologic phenomena predominate the non-immediate hypersensitivity category, and include maculopapular exanthema, drug eruptions, or more unusually, toxic epidermal necrolysis, and Stevens-Johnson syndrome [2-3]. Thus, pulmonary edema after RCM administration is rare and it is graded severe among the adverse clinical reactions [4]. We utilized Ioversol (Optiray 320, Mallinckrodt Canada ULC (Canada)) in our institution during coronary angiography for our patient. Ioversol is a non-ionic monomer. Although non-ionic RCM has a lower risk of eliciting adverse reactions than ionic RCM, our patient suffered from non-immediate pulmonary edema thereafter. Severe reactions, such as pulmonary edema and cardiac arrest, can occur in 0.04% of patients receiving non-ionic contrast media; in patients receiving ionic contrast media, the incidence may be 0.2% [5]. We do not know which RCM the local hospital utilized during the patient's prior coronary angiography. This may be a potential pitfall, as it could lower our threshold of awareness. A previous record of uneventful RCM administration may lead to the assumption that the patient has no hypersensitive predilections.

Pulmonary edema may be cardiogenic or non-cardiogenic through fundamentally different pathophysiologic mechanisms. In non-

cardiogenic pulmonary edema, permeability of the microvascular membrane increases due to direct or indirect lung injury, resulting in flooded, protein-rich alveoli [6]. Our patient underwent transthoracic echocardiogram shortly before coronary angiography, which disclosed fair cardiac output and no in-stent restenosis, and which in turn objectively supported a lower likelihood of heart failure. Also, the patient exhibited no signs of low cardiac output or peripheral edema. Chest roentgenogram showed a normal cardiac silhouette and no pleural effusion. Therefore, in view of all the evidence, non-cardiogenic pulmonary edema was highly probable. Non-cardiogenic pulmonary edema induced by nonionic low-osmolality RCM was first reported in 1995 [7]. Although rare, such pulmonary edema may be potentially life-threatening. Numerous case reports of non-cardiogenic pulmonary edema after intravenous RCM have been published [8]. A case report similar to that of our patient describing delayed hypersensitivity reaction manifesting as non-cardiogenic pulmonary edema, has improved after steroid treatment [9]. However, V-V ECMO was not utilized in the reported case. Thus, our patient's unexpected condition cannot be considered unprecedentedly. But, considering RCM-induced ARDS and salvage by ECMO, and even then undergoing LTx successfully, our patient may be a unique case. It is worthy emphasizing again the importance of distinguishing between cardiogenic and non-cardiogenic pulmonary edema, for the correct diagnosis will lead to correct treatment.

The Berlin Definition precisely describes the main features of ARDS [10]. ARDS may arise within 1 week of a known clinical insult or onset of new/worsening respiratory symptoms. In our patient, the trigger event was clearly the administration of Ioversol during coronary angiography. Chest imaging disclosed bilateral opacities that were not fully explained by effusions, lobar/lung collapse, or nodules. The origin of the edema, which caused respiratory failure, was not fully explained by cardiac failure or fluid overload. Impaired oxygenation further categorizes the patient into mild, moderate, or severe ARDS [11]. Our patient suffered from severe ARDS, given his PaO_2/FiO_2 ratio $\leq$100 under PEEP $\geq$5 cmH_2O. In patients with profound gas-exchange abnormalities, uncompensated hypercapnia with acidemia, despite ventilator support, is the classic presentation. When positive-pressure ventilation fails to maintain adequate oxygenation or carbon dioxide removal, ECMO can be initiated as salvage therapy [12]. The benefits of ECMO include direct removal of CO_2 from the blood, lowering delivered volumes from the ventilator, lowering the airway pressures required to deliver tidal breaths, and lowering the amount of FiO_2 needed, which are vaguely alluded to as a 'lung rest' or 'lung protective' strategy. Together, ECMO support and timely steroid administration contributed to our patient's recovery.

In conclusion, awareness of a delayed-type hypersensitivity reaction following non-ionic RCM exposure is crucial. Also, the ability to distinguish non-cardiogenic pulmonary edema from cardiogenic pulmonary edema can direct clinicians to the correct treatment strategy. V-V ECMO is not an ultimate resort, but a feasible tool offering support and salvage for the patient through times of crisis.

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顯影劑引發之急性呼吸窘迫症候群：案例報告

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顯影劑之過敏反應並非常見的臨床狀況，而致命之延遲性過敏反應更為臨床上所罕見。在此，我們報告的案例為一位 57 歲男性，診斷為原發性肺纖維化。病人為進行肺移植前評估，接受冠狀動脈造影術，術後病人的氧氣需求明顯增加，進而引發非心因性肺水腫。在釐清因果時，我們認為過敏反應比感染為更有可能之鑑別診斷。當病人病況惡化，呼吸器及純氧皆無法滿足病人的呼吸需求時，我們使用靜脈－靜脈體外膜氧合器以拮抗急性呼吸窘迫症候群，同時也審慎地使用類固醇治療。當這次非預期的延遲性過敏反應危機解除，病人逐漸康復，並於接受顯影劑施打的第二十九日後成功地接受肺臟移植。*(胸腔醫學 **2018; 33: 43-49**)*

關鍵詞：顯影劑，急性呼吸窘迫症候群，過敏反應

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