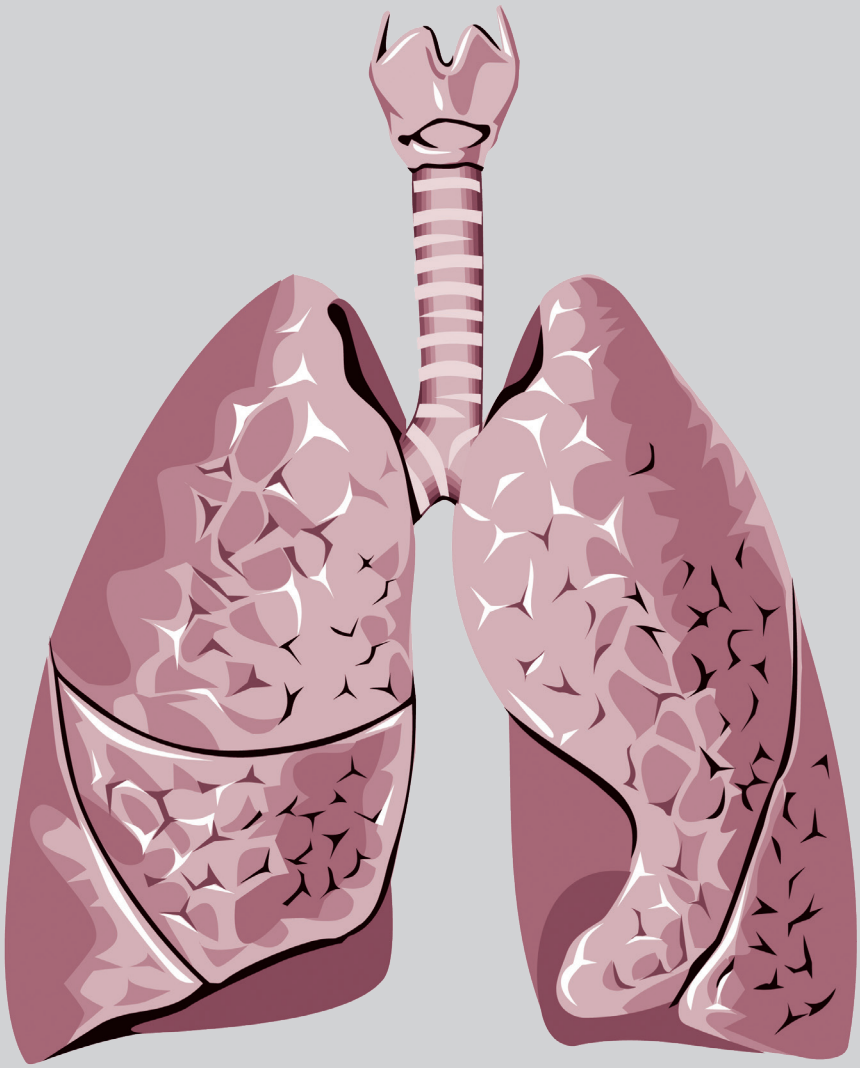
ISSN 1023-9855

Thoracic Medicine

Volume 40 • Number 3 • September 2025



The Official Journal of

Taiwan Society of Pulmonary and Critical Care Medicine

Taiwan Society of Sleep Medicine

Taiwan Society for Respiratory Therapy

Taiwan Society of Tuberculosis and Lung Diseases

Thoracic Medicine

The Official Journal of
Taiwan Society of Pulmonary and Critical Care Medicine
Taiwan Society for Respiratory Therapy
Taiwan Society of Sleep Medicine
Taiwan Society of Tuberculosis and Lung Diseases

Thoracic Medicine

The Official Journal of
Taiwan Society of Pulmonary and Critical Care Medicine
Taiwan Society for Respiratory Therapy
Taiwan Society of Sleep Medicine
Taiwan Society of Tuberculosis and Lung Diseases

Volume 40
Number 3
September 2025

CONTENTS

The Association Between Metformin Use and Outcomes of Hospitalized COVID-19 Patients

Chen-Yi Lin[1], Hsin-Pei Chung[1,3], Yen-Hsiang Tang[2,3], Chun-Yen Chen[3,4]
Chao-Hsien Chen[1,3], Wen-Kuei Chang[1,3], Kuan-Chih Kuo[1,3], Yen-Ting Chen[1,3]
Jou-Chun Wu[1,3], Chang-Yi Lin[1,3], Chieh-Jen Wang[1,3,*]

Background: Metformin is a widely prescribed medication for type 2 diabetes; however, therapeutic effects beyond glucose control have been reported. Recent studies have suggested its potential in alleviating symptoms of post-COVID-19 condition (long COVID), and possibly shortening the duration of the disease. We conducted this study to investigate whether metformin use could improve the outcomes of hospitalized COVID-19 patients.

Methods: We included patients diagnosed with COVID-19 infection at MacKay Memorial Hospital from May to June 2021. We categorized the patients into metformin and non-metformin use groups, regardless of their diabetes mellitus status.

Results: A total of 285 patients were included. After propensity score matching, 82 patients were enrolled for analysis, including 41 patients in each group. Cox proportional hazards analysis showed that mortality was not related to metformin use (adjusted hazard ratio [aHR]: 0.67, 95% confidence interval [CI]: 0.05-9.2, p=0.76) or duration of metformin use (aHR: 0.91, 95% CI: 0.74-1.13, p=0.40). However, patients with a longer duration of metformin use had a higher risk of receiving invasive mechanical ventilation support (aHR: 1.08, 95% CI: 1.03-1.13, p=0.003).

Conclusion: Our findings showed that mortality was not significantly associated with metformin use or its duration. However, patients with a longer duration of metformin use appeared to have a higher risk of requiring invasive mechanical ventilation support. Consequently, the duration of metformin use may be linked to the progression of COVID-19. Further studies are warranted to clarify the relevance of metformin use in the treatment of COVID-19. ***(Thorac Med 2025; 40: 194-201)***

Key words: Metformin, COVID-19, mortality, mechanical ventilation

[1]Division of Pulmonary, Department of Internal Medicine, MacKay Memorial Hospital, Taipei City, Taiwan. [2]Department of Critical Care Medicine, MacKay Memorial Hospital, Taipei, Taiwan. [3]Department of Medicine, MacKay Memorial Collage, New Taipei City, Taiwan. [4]Division of Cardiology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan.
Address reprint requests to: Dr. Chieh-Jen Wang, Division of Pulmonary, Department of Internal Medicine, MacKay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Zhongshan Dist., Taipei City, 104, Taiwan.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), first emerged in late December 2019 and rapidly evolved into a global pandemic. COVID-19 has had a great impact on both the individual and healthcare systems in many countries. Given the limited medical understanding and unprecedented nature of this disease, various pharmacologic interventions lacking proven effects, including chloroquine, lopinavir/ritonavir, favipiravir, interferon and tocilizumab, have been used in clinical settings [1]. In addition, metformin has also emerged as a potential treatment for COVID-19.

Metformin is a well-established agent used in the treatment of type 2 diabetes mellitus (DM), and it has had beneficial effects on COVID-19 patients in previous studies. The COVID-OUT study found that COVID-19 patients treated with metformin had a 41% lower incidence of long COVID [2]. Multiple mechanisms of action have been proposed for this effect, including reducing viral entry into the cell [3], and lowering anti-inflammatory activity and suppressing the release of proinflammatory cytokines [3-5]. Consequently, metformin may improve the outcomes of COVID-19 patients by reducing the symptoms associated with long COVID and shortening the overall disease duration [6]. Thus, we conducted this study to validate the potential impact of metformin on the outcomes of hospitalized COVID-19 patients.

Methods

Design and Patients

In this single-center, retrospective, observational study, we included adult patients diagnosed with COVID-19 infection at MacKay Memorial Hospital from May 1, 2021 to June 30, 2021. The inclusion criteria were patients aged 18 years or older, with a confirmed diagnosis of COVID-19 through a positive reverse transcription-polymerase chain reaction (RT-PCR) test at the emergency department. The exclusion criteria were patients with "do not intubate" orders and those with a history of previous COVID-19 diagnoses. Data on patient characteristics, medical conditions, co-morbidities, medication history, duration of hospitalization, and laboratory findings were obtained from a review of their electronic medical records. The Sequential Organ Failure Assessment (SOFA) score, a critical tool in assessing organ dysfunction and morbidity, was calculated for each patient.

The patients were assigned into metformin and non-metformin use groups, and the severity of disease, progression and hospital mortality rate were compared between the 2 groups. The metformin use group included patients with a record of metformin usage during hospitalization after being diagnosed with COVID-19 infection. To enhance the comparability of the groups and reduce the possible confounding effects of treatment selection bias, we performed 1:1 propensity score matching for age, gender and SOFA score for the 2 groups.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as percentages. Continuous variables were compared using Student's t test, and categorical variables were compared using the chi-square test or Fisher's exact test before and after matching. The duration of metformin use

was analyzed using receiver operating characteristic (ROC) curves. We used a Cox proportional hazards model to examine the association between metformin use and mortality, as well as the relationship between metformin use and the need for invasive mechanical ventilation (MV) support. We used the Kaplan–Meier method to plot survival curves, and analyzed differences between curves using the log-rank test. P-values <0.05 (2-sided) were considered statistically significant. Data were analyzed with SPSS version 21.0 (IBM, Armonk, NY, USA).

Results

A total of 332 patients were initially enrolled. After excluding 47 patients based on the exclusion criteria, a total of 285 patients were included. Among them, 41 patients were classified into the metformin use group, and 244 patients were classified into the non-metformin use group. Table 1 provides a detailed overview of the baseline characteristics of the patients, including demographics, medical history, and other relevant parameters. After 1:1 propensity

Table 1. Baseline Characteristics of Patients with/without Metformin use before (Unmatched) and after (Matched) 1:1 Propensity Score Matching

	Unmatched group			**Matched group**		
	Metformin use (n=41)	No metformin use (n=244)	*P* value	Metformin use (n=41)	No metformin use (n=41)	*P* value
Age (years)	62.3± 11.0	61.3± 15.4	0.69	62.3± 11.0	63.7±14.3	0.63
Gender (male)	24 (58.5%)	133 (54.5%)	0.63	24 (58.5%)	21 (51.2%)	0.51
SOFA score	2.0±1.5	2.2± 2.1	0.56	2.0±1.5	2.0±1.5	0.88
COPD	0 (0%)	13 (5.3%)	0.13	0 (0%)	1 (2.4%)	0.31
CAD	4 (9.8%)	17 (7.0%)	0.53	4 (9.8%)	3 (7.3%)	0.69
HF	0 (0%)	9 (3.7%)	0.21	0 (0%)	1 (2.4%)	0.31
DM	36 (87.8%)	48 (19.7%)	<0.001	36 (87.8%)	9 (22.0%)	<0.001
BMI	23.4±11.0	20.5±11.2	0.13	23.4±11.0	20.0±12.0	0.19
WBC	7207.3±3690.1	7742.6±8255.5	0.68	7207.3±3690.1	7339.0±4763.6	0.89
eGFR	78,7±34.6	75.9±37.0	0.66	78.7±34.6	76.8±33.7	0.81
Tocilizumab use	12 (29.3%)	74 (30.3%)	0.89	12 (29.3%)	11 (26.8%)	0.81
Remdesivir use	16 (39.0%)	94 (38.5%)	0.95	16 (39.0%)	17 (41.5%)	0.82
Metformin (days)	12.0±9.6	0		12.0±9.6	0	
MV use	11 (26.8%)	54 (22.1%)	0.51	11 (26.8%)	9 (22.0%)	0.61
Death	2 (4.9%)	24 (9.8%)	0.31	2 (4.9%)	2 (4.9%)	1.00
Propensity score	-1.76±0.13	-1.79±0.19	0.02	-1.76±0.13	-1.75±0.13	0.96

SOFA: sequential organ failure assessment; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; HF: heart failure; DM: diabetes mellitus; BMI: body mass index; WBC: white blood cells; eGFR: estimated glomerular filtration rate; MV: mechanical ventilation.

score matching to ensure balanced representation of patients in both groups, there were 41 patients each in the metformin use and non-metformin use groups.

Cox proportional hazards model analysis revealed that contrary to initial expectations, there was no statistically significant correlation between metformin use and mortality (adjusted hazard ratio [aHR]: 0.67, 95% confidence interval [CI]: 0.05-9.2, p=0.76). Moreover, there was no significant association between the duration of metformin use and mortality (aHR: 0.91, 95% CI: 0.74-1.13, p=0.40) (Table 2). However, those patients with a longer duration of metformin use during hospitalization had a higher risk of receiving invasive MV support (aHR: 1.08, 95% CI: 1.03-1.13, p=0.003), as shown in Table 3.

Table 2. Association between Metformin Use and Mortality Based on Cox Proportional Hazards Analysis

	Hazard ratio (95% CI)	*P* value
Unmatched group		
Model 1 Metformin (use vs. nonuse)	0.29 (0.06-1.34)	0.11
Model 2 Metformin use (days)	0.90 (0.78-1.02)	0.11
Matched group		
Model 1 Metformin (use vs. nonuse)	0.67 (0.05-9.20)	0.76
Model 2 Metformin use (days)	0.91 (0.74-1.13)	0.40

Variables in model 1: age, gender, metformin use (vs nonuse), DM
Variables in model 2: age, gender, metformin use (days), DM
DM: diabetes mellitus.

Table 3. Association between Metformin and Ventilator Use Based on Cox Proportional Hazards Analysis

	Hazard ratio (95% CI)	*P* value
Unmatched group		
Model 1 Metformin (use vs. nonuse)	1.10 (0.52-2.34)	0.80
Model 2 Metformin use (days)	1.04 (1.01-1.08)	0.03
Model 3 Metformin use (≥17.5 vs <17.5 days)	4.89 (1.91-12.51)	0.001
Matched group		
Model 1 Metformin (use vs. nonuse)	1.45 (0.47-4.46)	0.52
Model 2 Metformin use (days)	1.08 (1.03-1.13)	0.003
Model 3 Metformin use (≥17.5 vs <17.5 days)	7.94 (2.39-26.39)	0.001

Variables in model 1: age, gender, metformin use (vs nonuse), DM
Variables in model 2: age, gender, metformin use (days), DM
Variables in model 3: age, gender, metformin use (≥17.5 vs <17.5 days), DM
#cut-off point of 17.5 days was calculated using the ROC curve
DM: diabetes mellitus; ROC: receiver operating characteristic.

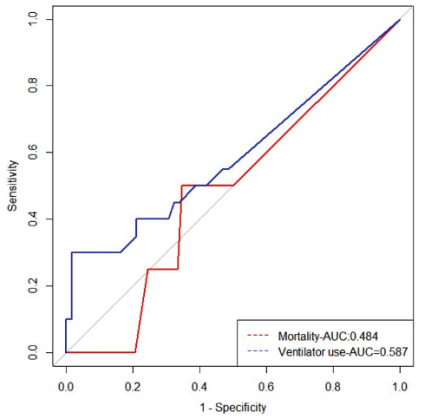


Fig. 1. Receiver Operating Characteristic Curve Analysis.
The area under the curve (AUC) for the association between metformin use and mortality was 0.484 (red line), and the AUC for the association between metformin use and the need for invasive mechanical ventilator support was 0.587 (blue line). Metformin use of 17.5 days was the optimal cut-off point.
AUC: area under the curve.

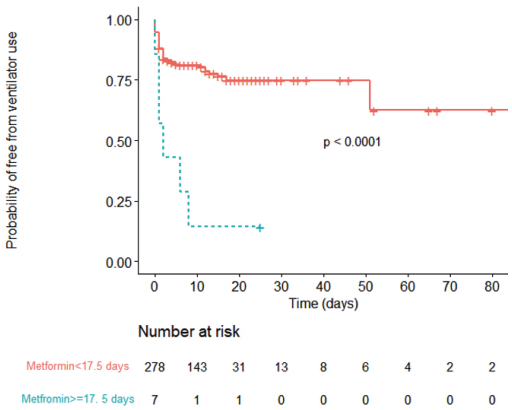


Fig. 2. Kaplan-Meier Analysis in the Unmatched Group.
The result showed that metformin use ≥17.5 days was correlated with a higher probability of receiving invasive mechanical ventilation support in the unmatched group.
Above: use "Probability of being free from ventilator use"; Metformin <17.5 days; Metformin >=17.5 days.

ROC curve analysis identified that the use of metformin for 17.5 days was an optimal cut-off point for comparisons. In addition, the area under the curve (AUC) for the association between metformin use and mortality was 0.484, and the AUC for the association between metformin use and the need for invasive MV support was 0.587 (Fig. 1). Kaplan-Meier analysis showed that metformin use ≥17.5 days was correlated with a higher probability of receiving invasive MV support in both the unmatched and matched groups (Fig. 2 and Fig. 3).

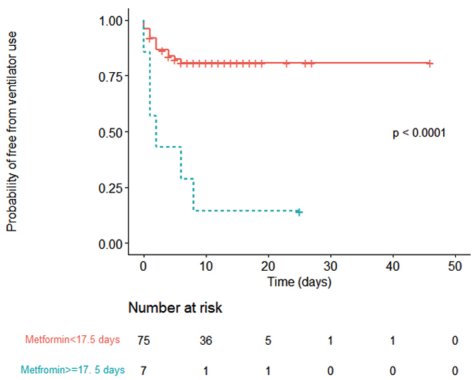


Fig. 3. Kaplan-Meier Analysis in the Matched Group.
The result showed that metformin use ≥17.5 days was correlated with a higher probability of receiving invasive mechanical ventilation support in the matched group.
Above: use the same corrections as in Fig. 2 above.

Discussion

Our results revealed no significant correlation between metformin use and mortality among COVID-19 patients. However, we observed an association between a longer duration of metformin use and the requirement for invasive MV support. These findings suggest that prolonged metformin usage may contribute to adverse outcomes in COVID-19 patients.

During the early stage of the COVID-19 pandemic, no standardized medications had yet been approved for its treatment. Consequently, various medications, including metformin, were explored as potential options. Although the use of metformin may seem unconventional in this context, there was evidence from systematic

articles illustrating its beneficial effects [7], including some efficacy in reducing the severity of COVID-19 [8].

Cytokine storm is a major factor contributing to the high mortality rate in COVID-19 patients [9]. Metformin has been observed to disrupt the function of proinflammatory cytokines by inhibiting the ACE-Ang II-AT1R signaling pathway [3], which reduces macrophage activation and NF-κB signaling. NF-κB signaling promotes the transcription of proinflammatory cytokines, including IL-1β, IL-6 and tumor necrosis factor alpha (TNF-α) [5]. Thus, by inhibiting the ACE-Ang II-AT1R signaling pathway, metformin can potentially inhibit the onset of a cytokine storm in the context of COVID-19 [10]. Some studies have shown that a cytokine storm can also be triggered by dysregulation of the AMPK/mTOR signaling pathway [11]. Metformin can activate AMPK, thereby suppressing the mTOR signaling pathway and consequently reducing pro-inflammatory signaling and the cytokine storm [12]. Activation of AMPK can also inhibit ACE2-viral spike protein binding, leading to a reduction in viral entry into the cell [4].

Clinical trials have also suggested an association between metformin use and a reduced risk of mortality [13]. In the COVID-OUT trial, metformin was shown to reduce the incidence of long COVID by 41%. In addition, metformin showed a more pronounced effect in reducing the risk of long COVID when initiated within 4 days of symptom onset [2]. However, our findings are not consistent with these clinical trials, and we found no association between metformin use and a reduction in mortality or improvement in COVID-19 symptoms. Moreover, we found an association between an increased risk of invasive MV use and a longer duration of metformin use during hospitalization. This raises important questions about the potential link between the duration of metformin use and a greater risk of requiring invasive MV in COVID-19 patients. In our study, metformin was administered exclusively to patients with DM. Further research is warranted to investigate the use of metformin as an independent treatment for COVID-19 in patients both with and without DM.

It is important to acknowledge that several factors are known to contribute to a higher risk of severe COVID-19, including pre-existing conditions such as DM, older age (>65 years), obesity (body mass index >30 kg/m2), cardiovascular disease, chronic lung disease, and liver disease [14]. These factors may influence the progression of the disease. Given that DM is associated with an immunocompromised status, we hypothesized that metformin users with DM may be more vulnerable to the progression of COVID-19 and consequent respiratory complications. This heightened vulnerability could potentially predispose them to an increased risk of requiring intubation as the disease advances. In addition, since we only recorded the duration of metformin usage during hospitalization, a longer duration of metformin use may have contributed to prolonged hospitalization. The association between prolonged metformin use and increased invasive MV may simply reflect the patient's unstable hemodynamic condition, necessitating extended hospitalization. This unstable condition likely increased the risk of requiring invasive MV.

There are some limitations to this study. First, it was a single-center, retrospective analysis. Second, we lacked data on the duration of metformin use in the patients prior to admission, and only recorded metformin usage dur-

ing hospitalization. As a result, our evaluation of metformin's impact on requiring mechanical support and on mortality was confined to the post-admission period. Third, we did not categorize our patients based on COVID-19 severity, such as mild, moderate, severe, or critical conditions. Additionally, in the metformin use group, we were unable to assess the severity of type 2 DM due to missing information on HbA1c levels, DM duration, or DM-related complications. These factors are crucial, as they could influence the outcomes related to the need for invasive MV and the mortality rates. Fourth, we did not increase the propensity score match ratio beyond 1:1 to enhance the precision of the study, because doing so could introduce higher bias. Fifth, immortal time bias may have skewed the results of this study, potentially affecting the accuracy of our findings. Patients were hospitalized following a confirmed COVID-19 diagnosis in the emergency department, and we only recorded the duration of metformin usage during hospitalization, up until discharge, death, or intubation. We did not account for the time between the confirmed diagnosis and the initiation of metformin use. Lastly, the decision to intubate and provide mechanical support was individualized for each patient, as there were no standardized criteria for selecting between invasive mechanical support and high-flow nasal continuous positive airway pressure as a means to delay intubation. Consequently, the number of patients requiring invasive MV support may have been underestimated.

Conclusion

Our results showed that the use of metformin was not associated with mortality among hospitalized COVID-19 patients. However, patients with an extended duration of metformin use had an increased risk of requiring invasive MV support.

References

1. Chen P-L, Lee N-Y, Cia C-T, *et al*. A review of treatment of coronavirus disease 2019 (COVID-19): therapeutic repurposing and unmet clinical needs. Front Pharmacol 2020; 11.
2. Bramante CT, Buse JB, Liebovitz DM, *et al*. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. Lancet Infect Dis 2023; 23(10): 1119-1129.
3. Malhotra A, Hepokoski M, McCowen KC, *et al*. ACE2, metformin, and COVID-19. iScience 2020; 23(9): 101425.
4. Samuel SM, Varghese E, Büsselberg D. Therapeutic potential of metformin in COVID-19: reasoning for its protective role. Trends Microbiol 2021; 29(10): 894-907.
5. Cory TJ, Emmons RS, Yarbro JR, *et al*. Metformin suppresses monocyte immunometabolic activation by SARS-CoV-2 spike protein subunit 1. Front Immunol 2021; 12.
6. Wise J. Covid-19: metformin reduces the risk of developing long term symptoms by 40%, study finds. BMJ 2023; 381: p1306.
7. Zangiabadian M, Nejadghaderi SA, Zahmatkesh MM, *et al*. The efficacy and potential mechanisms of metformin in the treatment of COVID-19 in the diabetics: a systematic review. Front Endocrinol (Lausanne) 2021; 12: 645194.
8. Erickson SM, Fenno SL, Barzilai N, *et al*. Metformin for treatment of acute COVID-19: systematic review of clinical trial data against SARS-CoV-2. Diabetes Care 2023; 46(7): 1432-1442.
9. Pence BD. Atypical monocytes in COVID-19: lighting the fire of cytokine storm? J Leukoc Biol 2021; 109(1): 7-8.
10. Taher I, El-Masry E, Abouelkheir M, *et al*. Anti-inflammatory effect of metformin against an experimental model of LPS-induced cytokine storm. Exp Ther Med 2023; 26(3): 415.

11. Maiese K. The mechanistic target of rapamycin (mTOR): novel considerations as an antiviral treatment. Curr Neurovasc Res 2020; 17(3): 332-337.
12. Kamyshnyi O, Matskevych V, Lenchuk T, *et al*. Metformin to decrease COVID-19 severity and mortality: molecular mechanisms and therapeutic potential. Biomed Pharmacother 2021; 144: 112230.
13. Guo Z, Gao Y, Xie E, *et al*. Effects of metformin on COVID-19 patients with type 2 diabetes: a retrospective study. Diabetes Metab Syndr Obes 2023; 16: 2573-2582.
14. Treskova-Schwarzbach M, Haas L, Reda S, *et al*. Pre-existing health conditions and severe COVID-19 outcomes: an umbrella review approach and meta-analysis of global evidence. BMC Med 2021; 19(1): 212.

Prognosis of *EGFR*-mutated Non-small Cell Lung Cancer Patients with Intra-abdominal Metastases

Hao-Ming Wu[1], Chi-Tsun Chiu[2], Jia-Shiuan Ju[1], Ping-Chih Hsu[1,3], Li-Chung Chiu[1,3]
Horng-Chyuan Lin[1,3], Cheng-Ta Yang[1,4,5], How-Wen Ko[1,3]

Background: Non-small cell lung cancer (NSCLC) patients generally have a poor prognosis with distant metastasis. Studies have found that NSCLC patients with epidermal growth factor receptor (*EGFR*) mutations exhibit a higher incidence of brain and bone involvement, which worsens prognosis. However, little is known about the outcomes of *EGFR*-mutated patients with intra-abdominal metastasis.

Materials and Methods: This retrospective study included 383 metastatic NSCLC patients with an *EGFR* mutation who received first-line gefitinib, erlotinib or afatinib at our hospital between January 2016 and December 2017.

Results: Ninety-eight patients (26%) had intra-abdominal metastasis, including liver (47), adrenal/renal (42), and abdominal lymph node/spleen (31) metastasis. In patients with intra-abdominal metastasis, overall survival (OS) (median, 17.5 vs. 32.7 months; $p < 0.001$) and progression-free survival (PFS) (median, 9.15 vs. 14.7 months; $p < 0.001$) were significantly shorter than in those without intra-abdominal metastasis. Compared to *EGFR*-mutated patients with only intra-thoracic metastasis (stage M1a), patients with intra-abdominal metastasis had the worse OS (hazard ratio (HR), 2.894; 95% confidence interval (CI), 2.051–4.082; $p < 0.001$), with the most severe reduction in OS in patients with adrenal/renal metastasis (HR, 5.646; 95% CI, 3.309–9.633; $p < 0.001$). No significant differences were observed in prognosis and response to first-line *EGFR*-TKIs between patients with an L858R mutation and those with an exon 19 deletion. The frequency of acquired T790M mutations was lower in patients with intra-abdominal metastases than in those without, but without statistical significance.

Conclusion: Intra-abdominal metastasis in *EGFR*-mutated NSCLC patients was associated with poor survival, with the worst outcomes in those with adrenal/renal metastasis.
(Thorac Med 2025; 40: 202-212)

Key words: Intra-abdominal metastasis, liver, adrenal, *EGFR*, NSCLC

[1]Division of Thoracic Medicine, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital, Taoyuan City 33305, Taiwan. [2]Institute of European and American Studies, Academia Sinica, Taiwan. [3]Department of Medicine, College of Medicine, Chang Gung University, Taoyuan City 33302, Taiwan. [4]Department of Internal Medicine, Taoyuan Chang Gung Memorial Hospital, Taoyuan City 33378, Taiwan. [5]Department of Respiratory Therapy, College of Medicine, Chang Gung University, Taoyuan City 33302, Taiwan.
Address reprint requests to: Dr. How-Wen Ko, Department of Thoracic Medicine, Chang Gung Memorial Hospital, No. 5, Fuxing St., Guishan Dist., Taoyuan 33305, Taiwan.

Introduction

Advanced non-small cell lung cancer (NSCLC) is associated with a poor prognosis and a high incidence of metastasis [1]. A significant proportion of NSCLC patients present with metastatic disease at diagnosis, and nearly half of those with early-stage lung cancer progress to metastatic disease within 5 years [2]. Major sites of NSCLC metastasis include bone (34.3%), lung (32.1%), brain (28.4%), liver (13.4%), adrenal glands (16.7%), and distant lymph nodes (9.5%) [3]. The prognosis of a separate metastatic organ in NSCLC has been extensively studied. It was reported that liver metastasis in NSCLC has the worst prognosis among lung cancer single organ metastases, with a median OS of 4 months [4]. On the other hand, NSCLC patients with adrenal metastasis were reported to have a lower OS than those without adrenal metastasis [5]. More research is needed to enhance the prognosis for patients with intra-abdominal metastasis.

Among the various genetic alterations identified in NSCLC, epidermal growth factor receptor (*EGFR*) mutations were present in nearly half of Asian NSCLC patients, but in only 11–16% of non-Asian patients [6]. With the development of *EGFR*-tyrosine kinase inhibitors (*EGFR*-TKIs), overall prognosis was much better in advanced NSCLC patients with *EGFR* mutations than in those with wild-type *EGFR* status [7]. Previous studies have suggested that *EGFR*-mutated NSCLC patients have a higher incidence of distant metastasis [8]. Intra-abdominal metastasis presents unique challenges due to the complex anatomical structures and the potential for multi-organ involvement [9]. However, less is known about the impact of intra-abdominal organ metastasis on the prognosis of NSCLC patients with *EGFR* mutations, such as to the liver, adrenal glands, or peritoneum.

In this study, we aimed to investigate the prognosis of *EGFR*-mutated NSCLC patients with intra-abdominal organ metastasis in a real-world cohort. In addition to treatment efficacy of first-line *EGFR*-TKIs, we also explored the association of different *EGFR* mutations with outcome, frequency of acquired T790M mutations, and outcome with later-line osimertinib treatment.

Materials and Methodss

This was a retrospective cohort study focused on patients with metastatic NSCLC. We recruited patients who received treatment in Linkou Chang Gung Memorial Hospital between January 2016 and December 2017. The inclusion criteria were newly diagnosed or recurrent metastatic NSCLC, positive *EGFR* mutations, and approval by Taiwan's National Health Insurance for first-line treatment with gefitinib, erlotinib or afatinib. All patients underwent a comprehensive staging assessment at diagnosis, which included computed tomography (CT) scans, positron emission tomography (PET) scans, and magnetic resonance imaging (MRI) of the brain.

Clinical data were recorded, including age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, histology, disease stage (according to American Joint Committee on Cancer, 8th edition), *EGFR* mutation types, first-line TKI treatment, osimertinib treatment, treatment duration, and initial metastasis prior to the administration of *EGFR*-TKI. Metastasis involving intra-abdominal organs (liver, renal/adrenal, abdominal lymph

node and spleen) was categorized as intra-abdominal metastasis. Participants were divided into 2 groups based on the presence or absence of intra-abdominal metastasis. All data of the enrolled patients were included in the analysis. The data cut-off for the final analysis was June 1, 2024.

This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (No. 202401317B0), and was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Statistical Analysis

Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazards regression model was utilized to estimate hazard ratios (HR) and 95% confidence intervals (CI) for both univariate and multivariate analyses, in order to identify factors affecting patient OS. Categorical variables were analyzed using the chi-squared test, and Student's t-test was used to compare continuous variables. For all analyses, a p value < 0.05 was considered indicative of a statistically significant difference. Statistical analyses were performed using R software (version 4.1.2).

Results

A total of 383 metastatic NSCLC patients with an EFGR mutation received TKI treatment. Baseline characteristics are summarized in Table 1. Ninety-eight patients (25.6%) had intra-abdominal metastasis, and had a similar age, gender composition, ECOG performance status, and smoking status to those without intra-abdominal involvement. However, a solitary lesion was uncommon upon diagnosis of intra-abdominal metastasis (TNM stage, M1b: 11.2%; M1c: 88.8%).

Among all stage IV NSCLC patients with *EGFR* mutations, those patients with intra-abdominal metastasis had significantly shorter OS (median, 17.5 months vs. 32.7 months; p < 0.001) and PFS (median, 9.15 months vs. 14.7 months; p < 0.001) than those without intra-abdominal involvement (Fig. 1). Stage M1a

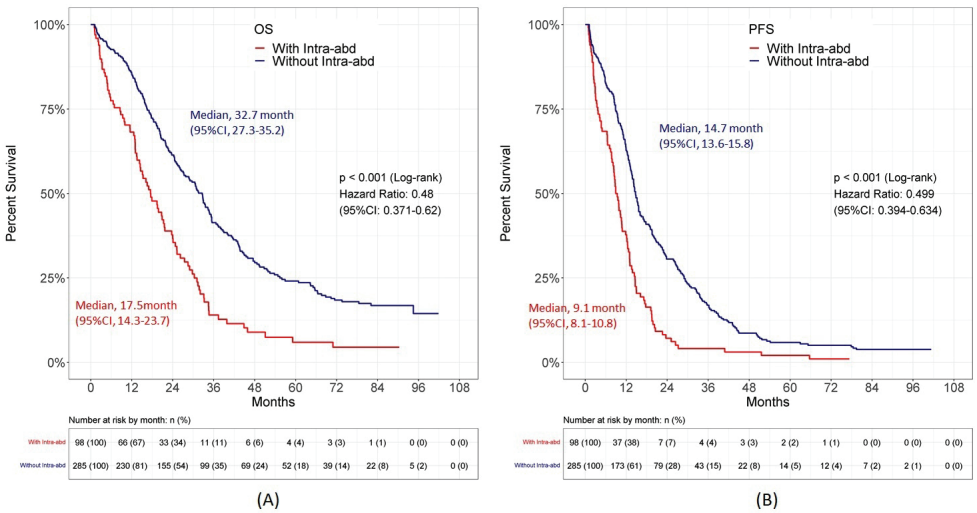


Fig. 1. OS (A) and PFS (B) in *EGFR*-mutated NSCLC patients with and without intra-abdominal metastasis. CI: confidence interval; *EGFR*: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; Intra-abd: intra-abdominal metastasis.

Table 1. Baseline Characteristics of all Metastatic *EGFR*-mutated NSCLC Patients

Demographic	All stage IV (n = 383)	With intra-abdominal metastasis (n = 98)	Without intra-abdominal metastasis (n = 285)	*P*-value
Age				
Mean ± SEM	66.1 (12.5)	65.9 (12.9)	66.2 (12.3)	0.793
Gender				
Male	152 (39.7%)	40 (40.8%)	112 (39.3%)	0.791
Female	231 (60.3%)	58 (59.2%)	173 (60.7%)	
ECOG PS				
0~1	321 (83.8%)	78 (79.6%)	243 (85.3%)	0.189
2~4	62 (16.2%)	20 (20.4%)	42 (14.7%)	
Smoking				
Never	308 (80.4%)	80 (81.6%)	228 (80.0%)	0.725
Ever	75 (19.6%)	18 (18.4%)	57 (20.0%)	
Histology				
Adenocarcinoma	365 (95.3%)	92 (93.9%)	273 (95.8%)	0.26
Adenosquamous	10 (2.6%)	2 (2.0%)	8 (2.8%)	
NSCLC, others	8 (2.1%)	4 (4.1%)	4 (1.4%)	
Stage				
M1a	111 (29%)	0 (0%)	111 (38.9%)	<0.001
M1b	51 (13.3%)	11 (11.2%)	40 (14.0%)	
M1c	231 (62.2%)	87 (88.8%)	132 (46.3%)	
Metastases				
lung/pleura/pericardia	282 (73.6%)	64 (65.3%)	218 (76.5%)	0.03
bone	180 (47%)	62 (63.3%)	118 (41.4%)	<0.001
brain	133 (34.7%)	44 (44.9%)	89 (31.2%)	0.014
intra-abdominal	98 (25.6%)			
liver	47 (12.3%)	47 (48%)	0	
adrenal/renal	42 (11.0%)	42 (42.9%)	0	
abdominal LNs/spleen	31 (8.1%)	31 (31.6%)	0	
***EGFR* mutations**				
19del	167 (43.6%)	44 (44.9%)	123 (43.2%)	0.453
L858R	185 (48.3%)	49 (50.0%)	136 (47.7%)	
Uncommon	31 (8.1%)	5 (5.1%)	26 (9.1%)	
1st-line EGFR-TKIs				
Gefitinib	59 (15.4%)	10 (10.2%)	49 (17.2%)	0.247
Erlotinib	88 (23.0%)	23 (23.4%)	65 (22.8%)	
Afatinib	236 (61.6%)	65 (66.3%)	171 (60.0%)	

ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; LN, lymph nodes; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; SEM: standard error of the mean

Table 2. Overall Survival of Patients with Various Distant Metastases Compared to Patients with Only Intra-thoracic Metastasis (M1a)

Site of metastasis	Compared to patients with only intra-thoracic metastasis (M1a)				
	mOS (mo)	HR	95% CI		*p* alue
			(lower	upper)	
M1a	35.4 (ref.)				
intra-abdominal	17.5	2.894	2.051	4.082	< 0.0001
liver	21.7	2.837	1.765	4.561	< 0.0001
adrenal/renal	14.3	5.646	3.309	9.633	< 0.0001
abdominal LNs/spleen	23.7	2.317	1.307	4.107	0.0040
brain	24.1	1.841	1.360	2.492	0.0005
bone	20.9	2.047	1.567	2.675	< 0.0001

M1a: TNM, M1a; mOS: median overall survival; mo: months; HR: hazard ratio; CI: confidence interval; LNs: lymph nodes

was defined as intra-thoracic metastasis, and included lung-to-lung and pleural/pericardial metastasis. Compared to stage M1a patients, patients with brain and bone metastasis, respectively, had poorer OS (HR: 1.841, 95% CI: 1.360 ~ 2.492, $p = 0.0005$; HR: 2.047, 95% CI: 1.567 ~ 2.675, $p < 0.0001$) (Table 2). Patients with intra-abdominal metastasis also had poorer OS (HR: 2.894, 95% CI: 2.051 ~ 4.082, $p < 0.0001$) and a relatively higher HR (Table 2), implying that intra-abdominal metastasis is a poor prognostic factor. Among the different types of intra-abdominal metastasis, adrenal/renal metastasis was associated with an even higher HR, suggesting that, among those with intra-abdominal metastasis, *EGFR*-mutated patients with adrenal/renal metastasis had a worse prognosis (Table 2).

Univariate and multivariate Cox regression analyses were also performed. Adrenal/renal metastasis was indeed identified as an independent unfavorable prognostic factor (Supplemental Table 1). In addition to adrenal/renal metastasis, bone metastasis was also associated with a poor prognosis.

In patients with intra-abdominal involvement, the incidence of an exon 19 deletion and an exon 21 L858R mutation was 44.9% and 50.0%, respectively. There was no significant difference in OS (median, 21.3 months vs. 15.3 months; $p = 0.20$) and PFS (median, 9.6 months vs. 9.85 months; $p = 0.720$) between these 2 groups (Fig. 2). Further analysis of the response to first-line *EGFR*-TKIs treatment showed no significant difference in OS (median, 13.5 months vs. 20.9 months; $p = 0.320$) and PFS (median, 8.4 months vs. 9.9 months; $p = 0.989$) between first-generation and second-generation treatment, with usage proportions of 33.6% and 66.3%, respectively (Fig. 3). Subsequent tissue and/or liquid biopsies were performed for the 169 patients upon disease progression after 1st-line treatment, and the acquired T790M mutation positivity rates in patients with and without intra-abdominal metastasis were 42.9% and 52.2%, respectively ($p = 0.348$) (Table 3). Eleven of the patients who developed the T790M mutation received osimertinib as second-line TKI treatment, with their OS (median, 21.3 months) and PFS (median, 14.5 months) presented in Fig. 4.

Supplemental Table 1. Univariate and Multivariate Analysis for Overall Survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
≥ 65	1.002	0.7970 ~ 1.260	0.985			
Sex						
Female	1.238	0.9776 ~ 1.568	0.077			
ECOG PS						
2~4	2.691	1.999 ~ 3.622	< 0.001	2.417	1.745 ~ 3.348	< 0.001
Smoking status						
Current/ex-smoker	0.983	0.736 ~ 1.313	0.908			
Histology						
Adenosquamous	1.716	0.911 ~ 3.229	0.094			
NSCLC, others	3.484	1.718 ~ 7.066	0.001	2.195	1.021 ~ 4.719	0.044
Metastasis						
M1b	1.627	1.109 ~ 2.387	0.013	1.239	0.787 ~ 1.950	0.355
M1c	2.031	1.527 ~ 2.702	< 0.001	1.123	0.689 ~ 1.831	0.641
Metastasis						
with lung/pleura/pericardia	0.932	0.724 ~ 1.1.99	0.582			
with bone	1.771	1.406 ~ 2.231	< 0.001	1.549	1.090 ~ 2.202	0.015
with brain	1.260	0.992 ~ 1.599	0.058			
with liver	1.592	1.138 ~ 2.227	0.007	1.459	0.989 ~ 2.154	0.057
with adrenal/renal	1.493	1.777 ~ 3.498	< 0.001	2.474	1.718 ~ 3.562	< 0.001
with abdominal LNs/spleen	1.290	0.849 ~ 1.961	0.223			
EGFR mutation						
Exon 19 deletion	0.643	0.505 ~ 0.820	< 0.001	0.718	0.555 ~ 0.928	0.011
Uncommon	1.416	0.926 ~ 2.165	0.108	1.783	1.142 ~ 2.782	0.011
First-line *EGFR*-TKI						
Erlotinib	1.124	0.777 ~ 1.626	0.534			
Afatinib	0.877	0.636 ~ 1.211	0.426			

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; LNs, lymph nodes.

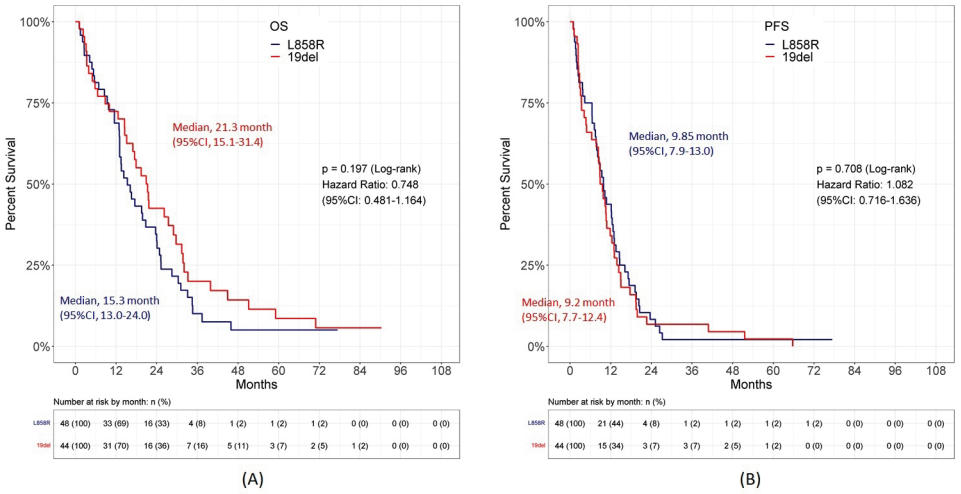


Fig. 2. OS (A) and PFS (B) in *EGFR*-mutated NSCLC patients with an exon 19 deletion or L858R mutation. CI: confidence interval; *EGFR*: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival.

Table 3. Frequency of Acquired T790M Mutation in Patients with and Without Intra-abdominal Metastasis

Acquired T790M	With intra-abdominal metastasis (n = 98)	Without intra-abdominal metastasis (n = 285)	*p* value
T790M detected	35	134	
T790M positive	15	70	
T790M negative	20	64	
T790M not detected	63	151	
T790M positive %	42.9%	52.2%	0.348

*T790M positive %: No. of T790M positive cases / No. of T790M detected cases x 100%

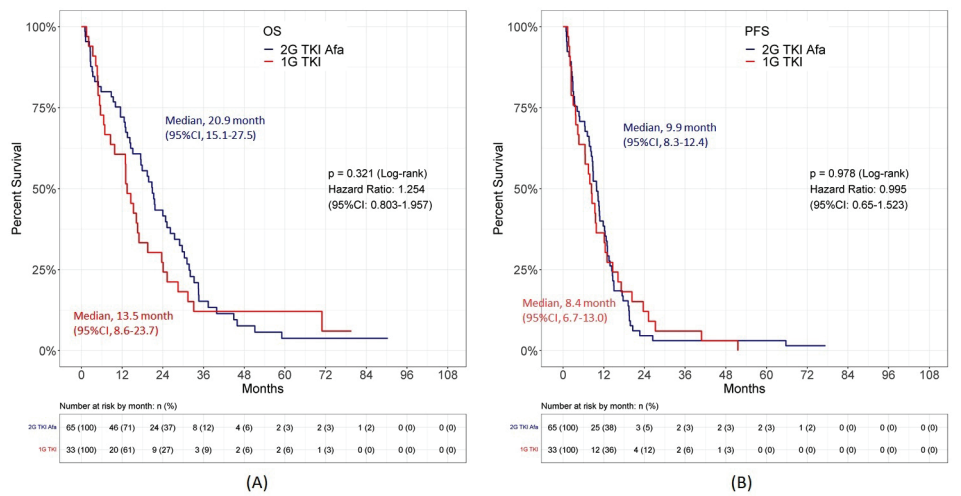


Fig. 3. OS (A) and PFS (B) in *EGFR*-mutated NSCLC patients treated with a first-generation or second-generation *EGFR*-TKI as 1st-line treatment. CI: confidence interval; *EGFR*: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; 1G: first generation; 2G: second generation; TKI: tyrosine kinase inhibitor; OS: overall survival; PFS: progression-free survival.

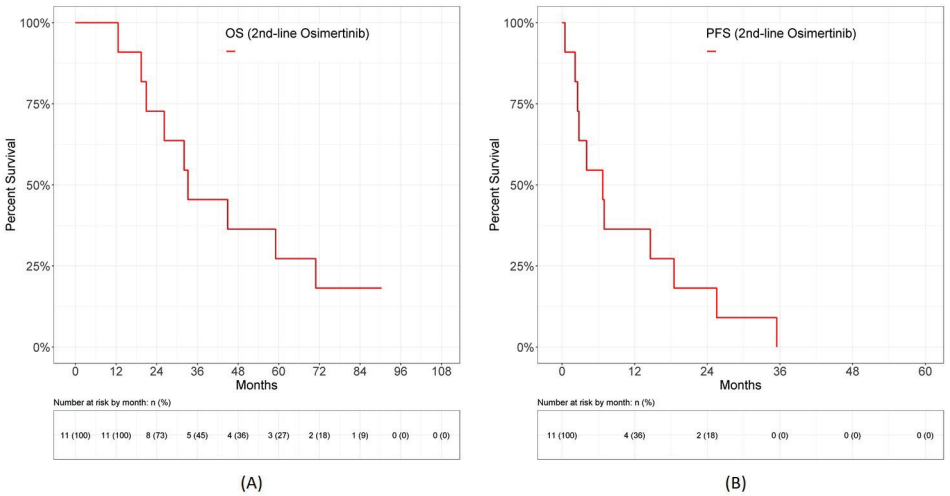


Fig. 4. OS (A) and PFS (B) in NSCLC patients with an EGFR mutation and intra-abdominal metastasis treated with 2nd and later-line osimertinib. CI: confidence interval; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival.

Discussion

Given the significant overlap in the vascular and lymphatic systems of the liver, adrenal glands, and intra-abdominal lymph nodes, as well as their anatomical proximity within the abdominal cavity, we proposed analyzing metastases to these areas as a distinct group. Our findings revealed that intra-abdominal metastasis in *EGFR*-mutated NSCLC patients was significantly associated with shorter OS, compared to patients without intra-abdominal metastasis. In the subgroup of patients of intra-abdominal metastasis, no significant differences in OS or PFS were observed between patients with different *EGFR* mutations or between patients treated with first-generation or second-generation *EGFR* TKIs.

Studies have shown that patients with *EGFR* mutations are more likely to develop distant metastasis, including to the brain, bone and liver [8, 10]. Additionally, NSCLC patients with distant metastasis are often linked to poor outcomes [11-13], a pattern confirmed in our analysis. Compared to stage M1a patients, those with intra-abdominal metastasis had shorter OS and a higher HR (median, 17.5 months vs. 35.4 months; HR: 2.894, 95% CI: 2.051 ~ 4.082, $p < 0.0001$), indicating that intra-abdominal metastasis may be an unfavorable prognostic marker. In our study population, those patients with intra-abdominal metastasis were more likely to have stage M1c disease, along with brain and bone metastasis, and less likely to have stage M1b or intra-thoracic metastasis. This suggested that *EGFR*-mutated patients with intra-abdominal metastasis tended to develop more widespread distant metastases, which may partly explain the association between intra-abdominal metastasis and poorer OS.

Little is known of post-adrenal/renal metastasis survival in *EGFR*-mutated patients treated with an *EGFR*-TKI. A retrospective study reported that 6% of *EGFR*-mutated NSCLC patients had adrenal/renal metastasis, a lower tendency than in patients with wild-type

EGFR (23%) [14]. Poor outcome was described with a median survival of 11 months [15]. In our study, 11% of patients had adrenal/renal metastasis, with OS and PFS of 13.4 and 8.75 months, respectively; both of these were shorter than in those without adrenal/renal metastasis. Multivariate Cox regression analysis also identified adrenal/renal metastasis as a poor prognostic factor. Some studies attempted to reverse this unfavorable prognosis through surgical resection. For instance, Buero, *et al*. suggested that adrenalectomy in patients with isolated adrenal gland metastasis may improve survival outcomes [16].

The liver is a common site of metastasis in NSCLC patients, with several studies reporting an incidence of liver metastasis ranging from 14% to 17% [5, 13]. Furthermore, it has been reported that NSCLC patients with *EGFR* mutations are more prone to developing liver metastasis [14]. In our subgroup analysis, 12.3% of patients had liver metastasis, a lower proportion than that reported in other studies. However, our study included patients with metastatic *EGFR*-mutated NSCLC exclusively, thereby limiting direct comparisons with patients without these mutations. This discrepancy also may be attributed to ethnic differences between the 2 study populations (white vs. Asian). Previous studies found that patients with liver metastasis had significantly poorer OS [4]. However, with treatment with *EGFR*-TKIs, the previously discouraging prognosis has undergone changes [9]. In our study, the OS and PFS of metastatic NSCLC patients with an *EGFR* mutation were consistent with previous findings [9], reflecting our structured treatment strategies and robust hospital support system.

Previous studies have shown that *EGFR* mutation status influences survival rates [7, 17]. Another study found that when the incidence rates of exon 19 deletions and L858R are comparable, exon 19 deletions are associated with better survival rates [18]. Our study similarly found comparable rates of L858R and exon 19 deletions, with a trend toward improved survival for patients with exon 19 deletions, although statistical significance may not always be achieved.

In the Lux-Lung 7 trial, afatinib significantly improved median PFS [19], but no significant difference in OS was observed compared to first-generation *EGFR*-TKI [20]. However, in our study, no significant differences in PFS or OS were observed between afatinib and first-generation *EGFR*-TKIs in patients with intra-abdominal metastasis. Given the retrospective nature of this study, the finding that PFS was closely aligned with time-to-treatment failure (TTF) in clinical practice may account for the discrepancies in the data.

The T790M mutation serves as a robust prognostic and predictive biomarker, indicating the greater efficacy of osimertinib [21], which is associated with significantly higher response rates, as well as extended PFS and OS in patients harboring this mutation [22]. In *EGFR*-mutated NSCLC-patients, the incidence of a T790M mutation in sequential biopsies has been reported to be around 50% [23], with a shorter OS observed in T790M-negative patients [23]. Though our cohort showed a shorter OS in patients with intra-abdominal metastasis, the incidence of acquired T790M mutation was 42.9% in 35 patients, with no significant difference compared to those without intra-abdominal metastasis (42.9% vs 52.2%, p=0.348). Osimertinib treatment in our study resulted in a median PFS and OS of 6.7 and 33.2 months, respectively, consistent with the results from the

AURA trials [24-25].

This study has several limitations. The primary limitation is its retrospective nature, which may have introduced selection bias. Second, the administration of sequential treatment could have influenced survival outcomes. Third, as osimertinib was not reimbursed as a first-line treatment prior to 2020, no patients in this study received osimertinib as a first-line therapy, creating a potential discrepancy between our results and current clinical practices. The poor prognosis indicates that further therapeutic studies for patients with intra-abdominal metastasis are urgently needed.

Conclusion

In summary, our study revealed an association between intra-abdominal metastasis and poor survival outcome in *EGFR*-mutated NSCLC patients. Among patients with intra-abdominal metastasis, those with adrenal/renal metastasis exhibited the worst outcomes. The poor prognosis indicates that further therapeutic studies for patients with intra-abdominal metastasis are urgently needed.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Chang Gung Memorial Foundation (No. 202401317B0). Participant consent was waved due to the retrospective nature of the study.

Availability of data and materials

The data sets analyzed in this study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare that they have no competing interests.

Author contributions

HWK, HCL and CTY conceptualized the study. HMW, JSJ, PCH and LCC collected the data. CTC conducted statistical analysis. HMW and HWK drafted the manuscript. All authors participated in designing the study, interpreting and analyzing the data, and reviewing the manuscript, and all authors approved the final version of the manuscript.

References

1. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res 2016; 5(3): 288-300.
2. Goldstraw P, Chansky K, Crowley J, *et al*. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016; 11(1): 39-51.
3. Tamura T, Kurishima K, Nakazawa K, *et al*. Specific organ metastases and survival in metastatic non-small-cell lung cancer. Mol Clin Oncol 2015; 3(1): 217-221.
4. Riihimäki M, Hemminki A, Fallah M, *et al*. Metastatic sites and survival in lung cancer. Lung Cancer 2014; 86(1): 78-84.
5. Ashour Badawy A, Khedr G, Omar A, *et al*. Site of metastases as prognostic factors in unselected population of stage IV non-small cell lung cancer. Asian Pac J Cancer Prev 2018; 19(7): 1907-1910.
6. Midha A, Dearden S, McCormack R. *EGFR* mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res 2015; 5(9): 2892-911.
7. Zhao D, Chen X, Qin N, *et al*. The prognostic role of *EGFR*-TKIs for patients with advanced non-small cell lung cancer. Sci Rep 2017; 7(1): 40374.

8. Kuijpers CCHJ, Hendriks LEL, Derks JL, *et al*. Association of molecular status and metastatic organs at diagnosis in patients with stage IV non-squamous non-small cell lung cancer. Lung Cancer 2018; 121: 76-81.
9. Jiang T, Cheng R, Zhang G, *et al*. Characterization of liver metastasis and its effect on targeted therapy in *EGFR*-mutant NSCLC: a multicenter study. Clin Lung Cancer 2017; 18(6): 631-639.e2.
10. Li H, Cao J, Zhang X, *et al*. Correlation between status of epidermal growth factor receptor mutation and distant metastases of lung adenocarcinoma upon initial diagnosis based on 1063 patients in China. Clin Exp Metastasis 2017; 34(1): 63-71.
11. Kuchuk M, Kuchuk I, Sabri E, *et al*. The incidence and clinical impact of bone metastases in non-small cell lung cancer. Lung Cancer 2015; 89(2): 197-202.
12. Ju J-S, Huang Allen C-C, Tung P-H, *et al*. Brain metastasis, *EGFR* mutation subtype and generation of *EGFR*-TKI jointly influence the treatment outcome of patient with *EGFR*-mutant NSCLC. Sci Rep 2023; 13(1): 20323.
13. Ko H-W, Chiu C-T, Wang C-L, *et al*. Overall survival improvement in patients with epidermal growth factor receptor-mutated non-small cell lung cancer and bone metastasis treated with denosumab. Cancers (Basel) 2022; 14(14).
14. Dormieux A, Mezquita L, Cournede PH, *et al*. Association of metastatic pattern and molecular status in stage IV non-small cell lung cancer adenocarcinoma. Eur Radiol 2020; 30(9):5021-5028.
15. Huang SH, Kong QL, Chen XX, *et al*. Adrenalectomy does not improve survival rates of patients with solitary adrenal metastasis from non-small cell lung cancer. Ther Clin Risk Manag 2017; 13: 355-360.
16. Buero A, Nardi WS, Chimondeguy DJ, *et al*. Outcomes of surgical treatment for isolated adrenal metastasis from non-small cell lung cancer. Ecancermedicalscience 2021; 15: 1322.
17. Huang C-Y, Chen B-H, Chou W-C, *et al*. Factors associated with the prognosis and long-term survival of patients with metastatic lung adenocarcinoma: a retrospective analysis. J Thorac Dis 2018; 10(4): 2070-2078.
18. Lin JJ, Cardarella S, Lydon CA, *et al*. Five-year survival in *EGFR*-mutant metastatic lung adenocarcinoma treated with *EGFR*-TKIs. J Thorac Oncol 2016; 11(4): 556-565.
19. Park K, Tan E-H, O'Byrne K, *et al*. Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016; 17(5): 577-589.
20. Paz-Ares L, Tan E-H, O'Byrne K, *et al*. Afatinib versus gefitinib in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 2017; 28(2): 270-277.
21. Eide IJZ, Helland Å, Ekman S, *et al*. Osimertinib in T790M-positive and -negative patients with *EGFR*-mutated advanced non-small cell lung cancer (the TREM-study). Lung Cancer 2020; 143: 27-35.
22. Ma J, Tan SH, Yin DXC, *et al*. Real world efficacy of osimertinib in second line/beyond in patients with metastatic *EGFR*+ non-small cell lung cancer and role of paired tumour-plasma T790M testing at tyrosine kinase inhibitor resistance. Transl Lung Cancer Res 2023; 12(4): 742-753.
23. Kuiper JL, Heideman DAM, Thunnissen E, *et al*. Incidence of T790M mutation in (sequential) rebiopsies in *EGFR*-mutated NSCLC-patients. Lung Cancer 2014; 85(1): 19-24.
24. Mok TS, Wu YL, Ahn MJ, *et al*. Osimertinib or platinum–pemetrexed in *EGFR* T790M–positive lung cancer. New Engl J Med 2017; 376(7): 629-640.
25. Papadimitrakopoulou V.A, Mok TS, Han J-Y, *et al*. Osimertinib versus platinum-pemetrexed for patients with *EGFR* T790M advanced NSCLC and progression on a prior *EGFR*-tyrosine kinase inhibitor: AURA3 overall survival analysis. Ann Oncol 2020; 31(11): 1536-1544.

Clinical Features of Thoracic Actinomycosis: Experience with 16 Cases at a Regional Hospital in Southern Taiwan

Wen-Ren Lin[1], Hui-Yuan Hsiao[2], Kuo-An Chu[1,3], Shoa-Lin Lin[2]

Background: Thoracic actinomycosis is a rare bacterial infection. This study aimed to enhance clinicians' knowledge of this rare condition in clinical practice.

Materials and Methods: We retrospectively analyzed 16 patients with histopathologically confirmed thoracic actinomycosis treated between 1995 and 2012.

Results: Almost all patients had a cough (87.5%, 14/16) with hemoptysis (75%, 12/16) or sputum (56.3%, 9/16). The radiographic picture included a speripheral mass or consolidation (68.8%, 11/16), pleuritis with or without effusion (43.8%, 7/16), and mediastinal lymphadenopathy (37.5%, 6/16). Five out of the 16 (31.3%) patients were diagnosed non-surgically, received medical therapy alone, and had excellent outcomes. Two patients exhibited endobronchial involvement associated with foreign bodies. All 16 patients responded well to penicillin, followed by ampicillin (8/16), amoxicillin (3/16), clindamycin (1/16), minocycline (2/16), erythromycin (1/16), or no antibiotic treatment (1/16). The patients??? had a good prognosis with no relapse.

Conclusion: Foreign body-induced endobronchial infection responded favorably to foreign body removal and a short course of antibiotics. Medical therapy alone is often sufficient for a cure. When encountering this condition, the pulmonologist should consider the probability of actinomycosis, then diagnose the condition least invasively, thereby avoiding unwarranted surgery. ***(Thorac Med 2025; 40: 213-221)***

Key words: actinomycosis; bronchoscopy; pathology; pulmonary; thoracic disease; treatment

Introduction

Actinomycosis is a subacute-to-chronic bacterial infection caused by filamentous Gram-positive, non-acid-fast, anaerobic-to-micro-aerophilic bacteria, and is characterized by contiguous spread, suppurative granulomatous inflammation, or multiple abscess formation. Thoracic actinomycosis accounts for 15–20% of all actinomycosis cases [1-2]. Aspiration

[1]Division of Chest Medicine, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan. [2]Division of Chest Medicine, Department of Internal Medicine, Yuan's General Hospital, Kaohsiung, Taiwan. [3]National Yang-Ming University School of Medicine, Taipei, Taiwan.
Address reprint requests to: Dr. Hui-Yuan Hsiao, Division of Chest Medicine, Department of Internal Medicine, Yuan's General Hospital, No. 162, Chenggong 1st Road, Kaohsiung City 802, Taiwan.

of oropharyngeal secretions containing actinomycetes is the usual mechanism of infection. However, thoracic actinomycosis occasionally results from the introduction of organisms via esophageal perforation, direct spread from an actinomycotic process of the neck or abdomen, or hematogenous spread from a distant lesion [3]. Thoracic actinomycosis commonly presents as a pulmonary infiltrate or mass, which, if left untreated, can spread to the pleura, pericardium, and chest wall, ultimately leading to the generation of sinuses that discharge sulfur granules [2, 4].

Owing to its chronic development, chest radiographic presentations, and nonspecific laboratory findings, thoracic actinomycosis has often been misdiagnosed as a neoplasm or tuberculosis (TB) [1]. Pulmonary actinomycosis currently is a rare condition -- a previous report found only 4 cases of histologically diagnosed pulmonary actinomycosis over 15 years in a large 1,100-bed teaching hospital in Nottingham, UK [1]. This retrospective study describes the clinical features of thoracic actinomycosis in 16 patients that presented over a 17-year period at a tertiary teaching hospital in southern Taiwan.

Materials and Methods

We identified adult patients diagnosed with thoracic actinomycosis at Kaohsiung Veterans General Hospital between November 1995 and April 2012, and included those who fulfilled the following inclusion criteria in this retrospective study: (1) Pulmonary parenchymal abnormalities on computed tomography (CT). (2) Histopathological identification of actinomycosis in tissues obtained by lung resection, bronchial biopsy, or transthoracic lung biopsy. All patients had pathologically confirmed Actinomyces infection based on histopathological findings of sulfur granules or Grocott-Gomori methenamine silver stain-positive branching filamentous organisms. Specimens were obtained using surgical biopsy, bronchoscopic protective sheath brushing, or percutaneous fine-needle core biopsy.

The exclusion criteria were age < 18 years, medical records without sufficient data, and a previous diagnosis of actinomycosis before admission.

The requirement for written informed consent was waived due to the retrospective nature of the study, and the data were analyzed anonymously. This study was approved by the Institutional Review Board of Yuan's General Hospital (protocol number 20221107 B).

The medical charts, including information regarding age, sex, presenting symptoms, comorbidities, Table 1 diagnostic methods, thera-

Table 1. Diagnostic Method

	Number (%)
Pathology	14 (87.5)
Cytology	2 (13.3)
Bronchoscopy	4 (26.6)
CT-guided biopsy	1 (6.6)
Chest wall biopsy	1 (6.6)
Surgical lung biopsy	10 (62.5)

peutic modalities, duration of intravenous or oral antibiotic treatment, and clinical outcomes of all 16 patients included in this study, were reviewed. We also examined the study participants' initial and follow-up chest radiographs and chest CT scans, and considered lymph nodes greater than 1 cm in transverse diameter on CT images as enlarged. Chest X-ray features were categorized as non-segmental pneumonia-like infiltration, mass-like consolidation, abscess formation, cavitation, pleural effusion or thickening, atelectasis, and chest wall extension based on the predominant features [5]. Clinical cure was defined as the resolution of clinical symptoms and the disappearance or reduction of residual scarring of the primary lesion on the pulmonary image. All patients were stable and without recurrence at the 3-year follow-up.

Results

The 16 patients with thoracic actinomycosis included 12 men and 4 women. The mean patient age was 51 years (range: 24–73 years). Table 2 presents detailed information regarding the clinical features of the patients. Eight patients had a history of smoking, and 4 had an underlying pulmonary comorbidity, including 3 with bronchiectasis and 1 with chronic obstructive pulmonary disease (COPD). The most common underlying conditions were poor oral hygiene, affecting 9 patients (56.3%), and diabetes mellitus, affecting 6 patients (37.5%). One patient (6.3%) had psoriasis with an underlying immunosuppressive disease and was receiving corticosteroid therapy.

Cough, hemoptysis, and productive sputum were the 3 most common symptoms, and the duration of these symptoms in all 16 patients was 5.6 months. Only 5 patients presented with fever (5/16, 31%). The mean values of serum C-reactive protein and white blood cell counts were 22.8 mg/dl and 12.1 x 109/L, respectively. The most common suspected diagnosis was pulmonary malignancy (50%), followed by TB (25%) and pneumonia or pneumonitis (12.5%). Table 3 presents data on the chest X-rays and CT images of all patients. The most common radiographic finding was peripheral consolidation or mass (68.8%) (Fig. 1). Most lesions showed a mid-zone predilection (56.3%), and 7 patients' lesions (43.8%) were in the right lobe. Mediastinal or hilar lymph node enlargement and pleural invasion were noted in 6 (37.5%) and 7 (43.8%) patients, respectively. Chest wall destruction was present in 3 patients (18.8%); however, severe complications such as empyema, chest wall sinus fistula, pericarditis, or mediastinitis did not occur in our cases.

All 16 patients were initially misdiagnosed. Lung cancer was the most common initial diagnosis, noted in 8 (50%) patients, followed by pulmonary TB in 4 (25%). Other misdiagnoses include organizing pneumonia, pneumonitis, atelectasis, and abscesses. The sputum cultures tested negative for actinomycosis.

Actinomycosis was histopathologically confirmed in all 16 patients, 10 of whom (62.5%) received wedge resection or lobectomy, and 4 (25%) underwent transbronchial lung biopsy and/or brushing. CT-guided transthoracic cutting-needle core biopsy was successful in 1 patient (6.3%), and needle aspiration biopsy of the chest wall in another patient (6.3%). All patients had histopathological findings of sulfur granules or Grocott-Gomori methenamine silver stain-positive branching filamentous organisms.

Four of the 11 patients who underwent bronchoscopic examination had a confirmed diagnosis. Seven patients exhibited signs of bron-

Table 2. Clinical Features of the 16 Patients with Confirmed Thoracic Actinomycosis

	Number (%)
Male sex	12 (75)
Age (years)	51 [24-73]
Body mass index (kg/m^2)	21.7 [19-30.2]
History of smoking	8 (50)
Dental status	
Carious	9 (56.2)
Normal	4 (25.0)
Not known	3 (18.7)
Laboratory values	
C-reactive protein (mg/dl)	22.8 [3.6-30]
White blood count (cells x10^9/L)	12.1 [8.3-23.5]
Underlying disease	
Diabetes mellitus	6 (37.5)
Viral hepatitis (HBV or HCV)	4 (25.0)
Alcohol abuse	3 (18.7)
Bronchiectasis	3 (18.7)
Malignancy	1 (6.2)
COPD	1 (6.2)
Steroid use	1 (6.2)
None	5 (31.2)
Symptoms	
Respiratory	
Cough	14 (87.5)
Hemoptysis	12 (75)
Productive sputum	9 (56.2)
Chest pain	6 (37.5)
Located swelling of chest wall	4 (25.0)
Dyspnea	3 (18.7)
Systemic	
Fever	5 (31.2)
Weight loss	4 (25.0)
Duration of symptoms (months)	5.6 (0.6-18)
Suspected diagnosis for hospitalization	
Malignancy	8 (50.0)
Tuberculosis	4 (25.0)
Pneumonia/pneumonitis	2 (12.5)
Atelectasis	1 (6.2)
Abscess	1 (6.2)

Note: the [brackets] above are used to indicate the range of each variable.

Table 3. Image Findings of the 16 Cases of Thoracic Actinomycosis

	Number (%)
Site of lesions	
Right	7 (43.8)
Left	5 (31.2)
Bilateral/Multifocal	4 (25.0)
Upper zone	1 (6.2)
Mid zone	9 (56.3)
Lower zone	7 (43.7)
Radiographic features	
Peripheral mass/consolidation	11 (68.7)
Pleuritis	7 (43.8)
Mediastinal lymphadenopathy	6 (37.5)
Central mass with atelectasis	5 (31.2)
Abscess/infected cavity	4 (25.0)
Chest wall invasion	3 (18.8)
Bronchiectasis	1 (6.2)

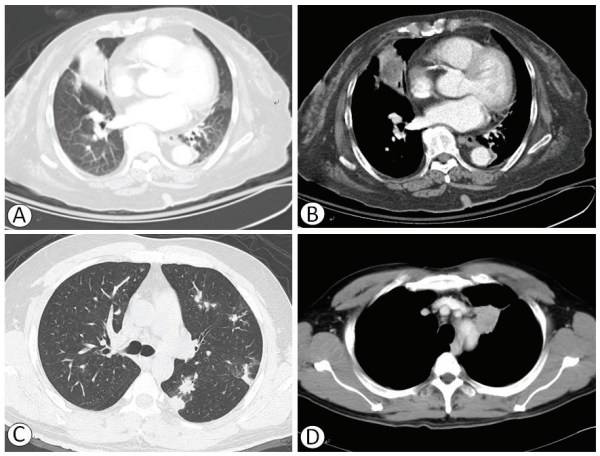


Fig. 1. Different manifestations of pulmonary actinomycosis on chest computed tomography. (A) A 78y/o female presented at our hospital with chronic cough and generalized weakness. Lung cancer was suspected initially. Consolidation of the right middle lobe with central necrosis in the right lower lobe anterior basal segment was seen in 1 patient, and (B) central low attenuation was noted with a mediastinal window setting; (C) A 38 y/o male presented with productive cough for several months. Multiple ill-defined irregular nodular lesions at both lungs were seen on computed tomography; (D) A 51 y/o male presented with dry cough for several months. A soft tissue lesion with post-contrast homogeneous enhancement was seen in the left upper lobe.

chial inflammation, such as swelling-related luminal narrowing, easy contact bleeding, whitish secretions, and granulation tissues; findings were unremarkable in the other 4 patients. Of the 2 cases with endobronchial foreign bodies, 1 was confirmed to be a fishbone at the right lower lobe bronchus, and the other, an incisor at the left lower lobe bronchus. In both cases, the foreign body obstructed the bronchi and granulation tissue.

Empiric antibiotics were administered after confirming the pulmonary actinomycosis diagnosis. Of the several antibiotics used to treat pulmonary actinomycosis, ampicillin was most commonly used (8 patients), followed by penicillin G (6 patients), amoxicillin (3 patients), and minocycline (2 patients). Other antibiotics were occasionally used, including clindamycin and erythromycin (1 patient each).

After diagnosing actinomycosis, we initiated intravenous antibiotic treatment followed by oral antibiotics. The mean duration of treatment with intravenous and oral antibiotics was 15.6 days (range: 7–28 days) and 129.7 days (range: 21–308 days), respectively. However, 1 of the 16 patients did not receive antibiotics, and curative treatment included bronchoscopic removal of the endobronchial foreign body and surgical lobectomy. During follow-up periods ranging from 1 month to 3 years, all patients had documented clinical and radiological remission at the end of therapy.

Discussion

In this study, we analyzed 16 patients with histopathologically confirmed thoracic actinomycosis. Our goal was to assist clinicians in promptly and accurately diagnosing thoracic actinomycosis to avoid unnecessary surgical interventions.

Although actinomycosis affects individuals of all ages, previous case series indicate a peak incidence during middle age, and males are 3 times more frequently infected than females [1, 6-8]. Our study revealed that the highest incidence occurred during the 4th and 5th decades of life, with a male-to-female [[ratio of 3:1]], consistent with previous reports [1, 6-8]. A foreign body was found and extracted using bronchoscopy in 2 patients older than 70 years with a history of frequent choking. The youngest patient was aged 24 years and had a history of heavy alcohol consumption.

Actinomyces commonly inhabit the oropharynx, and pulmonary infection typically results from aspiration of oropharyngeal secretions containing these bacteria. Recognized risk factors include poor oropharyngeal or dental hygiene, alcoholism, and advanced age with dysphagia. Another risk factor is the presence of devitalized lung tissue due to an underlying chronic lung disease. According to our data, 9 patients (56.2%) had carious teeth with or without poor oral hygiene, and 3 patients (18.8%) were alcohol abusers. Furthermore, pre-existing pulmonary comorbidity was noted in 4 cases (25%), including 1 case of COPD and 3 cases of bronchiectasis. Eight patients (50%) were current or former smokers, which was a lower percentage compared to rates reported in other series (61–70%) [6-8]. In addition, 6 of our patients (37.5%) had diabetes mellitus, which was also a considerable factor in some other series [6, 9]. Furthermore, all case series on pulmonary actinomycosis reported either a remarkable absence or a low proportion of immunocompromised patients. While most of our patients were immunocompetent, 1 patient, who received oral corticosteroids for psoriasis maintenance, was relatively immunocompromised. More than one-quarter of our patients had chronic hepatitis B or C, a comorbidity never mentioned in other studies, the significance of which remains unclear and warrants further investigation.

The symptoms of thoracic actinomycosis are nonspecific and include a variety of pulmonary and systemic complaints that often mimic the features of neoplastic diseases or TB. In a recent series, the predominant symptoms included cough, sputum, hemoptysis, chest pain, weight loss, and fever. Systemic complaints developed in 20–26% of patients. Chest pain was more frequently seen in the European series, while hemoptysis was more common in the Asian series [10]. Our study revealed a high incidence of hemoptysis (75%), even higher than that of productive sputum (62.5%). Tenderness and chest wall edema were found in 6 (37.5%)

and 4 (25%) patients, respectively, reflecting varying clinical presentations in different regions. Given the chronic nature of this infection, its nonspecific presentation, and the regular suspicion of alternative lung disease at first presentation, the symptom duration lasted up to 72 months before diagnosis in a recent case series, with a mean duration of 10 months [11]. In another European report, the mean duration of illness before a definitive diagnosis was approximately 6 months [1]. The mean symptom duration in this study was 5.6 months, consistent with previous reports [1, 11]. Several factors, including chronic infection characteristics, nonspecific symptoms, and lack of recognition by general physicians, may have extended the duration from initial symptom onset to the ultimate diagnosis of thoracic actinomycosis. Additionally, patients in southern Taiwan tend to be more concerned about invasive examination procedures, so this could delay the diagnosis.

Chest CT is essential for better differentiation and planning of invasive diagnostic procedures. CT scans may reveal necrotic low-density areas within parenchymal consolidations, adjacent pleural thickening, and mediastinal lymph node enlargement in up to 50% of cases [10, 13, 15]. Our study highlighted right-side parenchymal consolidation or masses, pleurisy, and mediastinal lymphadenopathy as predominant radiological features. A central mass with atelectasis was noted in 5 patients following bronchoscopy, confirming endobronchial involvement, and included stenosis, swelling, and a foreign body. Diagnostic confirmation of thoracic actinomycosis typically relies on a combination of risk factors, including compatible clinical and radiological presentations, detection of sulfur granules in infected tissue, and microbiological confirmation through tissue culture. However, cultures may yield negative results in most cases because of empirical antimicrobial pre-treatment, associated bacterial overgrowth, and the fastidious nature of actinomycetes [1, 10]. Diagnostic confirmation is often achieved in clinical practice through a typical histopathological picture, including sulfur granules in infected tissues [10, 16]. All patients were diagnosed based on these histopathological features and achieved complete remission after adequate management.

Invasive procedures are required to obtain adequate samples for microbiological and histological analysis. As observed in our study, frequent suspicion of a pulmonary malignancy often leads to diagnostic surgical procedures. However, with the increasing availability of less invasive options, such as image-guided transthoracic needle biopsy or bronchoscopic techniques, the frequency of the use of surgical procedures for diagnostic confirmation has been reduced, based on data from many recently published series [10, 17]. Given that effective antibiotic treatment is associated with a favorable prognosis, even in complicated cases, a diagnostic strategy that avoids surgery may prevent considerable morbidity, discomfort, cost, and diagnostic delay [10]. In our study, 6 patients (37.5%) who underwent non-surgical diagnostic intervention received optimal medical treatment and achieved outcomes as favorable as those of the surgical group.

Antibiotic treatment is highly effective for thoracic actinomycosis, especially when diagnosed early. Penicillin remains the drug of choice, with 20–30 million units per day administered for the first 2–6 weeks, followed by a prolonged period of oral therapy with penicillin V. Although penicillin allergy is a crucial limitation, doxycycline, macrolides, and clindamycin

have been successfully used as alternatives [7, 15]. Recent reviews recommend a total duration of 6–12 months of antibiotic therapy [1, 18]. However, accumulating evidence suggests that individualized shorter courses (< 6 months) of treatment are associated with good clinical outcomes [6]. In our study, 7 patients were treated for less than 4 months, 11 underwent surgical resection, and 2 underwent endobronchial foreign body extraction. Important factors to consider are radiographic evidence of reduction of the primary lesion within the first 2–3 months of treatment and the duration of symptoms before diagnosis. Intensive clinical follow-up after the end of treatment, especially in patients treated for a short period (< 3 months) and those with a complicated disease presentation, is crucial for detecting possible disease recurrence or local complications [10].

Endobronchial actinomycosis is a rare type of thoracic actinomycosis associated with bronchiolitis, TB, or a foreign body [7-8]. In the bronchoscopic exam, it presents as a necrotic, whitish, or yellowish endobronchial mass or irregular granular thickening mimicking a tumor. Granulomatous processes can cause airway narrowing or complete bronchial obstruction [16]. In the present study, 2 patients had endobronchial actinomycosis associated with a foreign body, and after removing the causative foreign body, 1 month of antibiotic treatment led to a clinical and radiological cure. Umeki and Maki reported successful resolution of foreign body-induced endobronchial actinomycosis within less than 1 month of penicillin G administration in combination with bronchoscopic removal of the foreign body [7]. Bronchoscopy is an essential tool for diagnosis and treatment, and in the absence of a foreign body, most cases of endobronchial actinomycosis can be cured with antibiotics [7, 16, 18].

All patients achieved clinical and radiological cures without therapeutic surgery. Thoracic actinomycosis is a medical condition in which antibiotic therapy often leads to complete recovery. Thus, primary surgical intervention should be reserved for patients who develop complications such as massive hemoptysis or empyema, those who do not respond well to medical treatment, or those for whom a medical diagnosis cannot be established [10, 13].

Conclusion

Early diagnosis may prevent critical complications and unnecessary surgery. Bronchoscopy plays a crucial role in the diagnosis of suspected endobronchial lesions. High-dose and long-term (6- to 12-month) penicillin or amoxicillin treatment remains the therapy of choice. However, the duration of antibiotic treatment can be individualized according to the resolution of symptoms and radiological lesions. Pulmonary actinomycosis is a rare bacterial infection often misdiagnosed as lung cancer or pulmonary TB. The definitive diagnosis depends on the pathology; sulfur granules are suggestive but not specific. Penicillin G was used as a standard treatment. However, the optimal antibiotic treatment duration requires further investigation.

References

1. Mabeza GF, Macfarlane J. Pulmonary actinomycosis. Eur Respir J 2003; 21(3): 545-51.
2. Hsieh MJ, Liu HP, Chang JP, *et al*. Thoracic actinomycosis. Chest 1993; 104(2): 366-70.
3. Apothéloz C, Regamey C. Disseminated infection due to Actinomyces meyeri: case report and review. Clin Infect Dis 1996; 22(4):621-5.

4. Webb WR, Sage SS. Actinomycosis involving the chest wall: CT findings. Am J Roentgenol 1982; 139(5): 1007-9.
5. Poey C, Giron J, Verhaegen F, *et al*. X-ray computed tomographic and radiographic aspects of thoracic actinomycosis. J Radiol 1996; 77(3): 177-83.
6. Wong VK, Turmezei TD, Weston VC. Actinomycosis. BMJ 2011; 343: d6099.
7. Maki K, Shingawa N, Nasuhara Y, *et al*. Endobronchial actinomycosis associated with a foreign body--successful short-term treatment with antibiotics. Intern Med 2010; 49(13): 1293-6.
8. Bergthorsdottir R, Benediktsdottir KB, Thorsteinsson SB, *et al*. Endobronchial actinomycosis secondary to a tooth aspiration. Scand J Infect Dis 2004; 36(5): 384-6.
9. Brown JR. Human actinomycosis. A study of 181 subjects. Hum Pathol 1973; 4(3): 319-30.
10. Rohde G, Subotic D. eds. Complex Pleuropulmonary Infections: European Respiratory Monograph. 2013: European Respiratory Society.
11. Sun XF, Wang P, Liu HR, *et al*. A retrospective study of pulmonary actinomycosis in a single institution in China. Chin Med J (Engl) 2015; 128(12): 1607-10.
12. Kim SR, Jung LY, Oh In-Jae, *et al*. Pulmonary actinomycosis during the first decade of 21st century: cases of 94 patients. BMC Infect Dis 2013; 13: 216.
13. Song JU, Park HY, Jeon K, *et al*. Treatment of thoracic actinomycosis: a retrospective analysis of 40 patients. Ann Thorac Med 2010; 5(2): 80-5.
14. Valour F, Senechal A, Dupieux C, *et al*. Actinomycosis: etiology, clinical features, diagnosis, treatment, and management. Infect Drug Resist 2014; 7:183-97.
15. Han, JY, Lee KN, Lee JK, *et al*. An overview of thoracic actinomycosis: CT features. Insights Imaging 2013; 4(2): p. 245-52.
16. Chouabe S, Perdu D, Deslee G, *et al*. Endobronchial actinomycosis associated with foreign body: four cases and a review of the literature. Chest 2002; 121(6): 2069-72.
17. Kolditz M, Bickhardt J, Matthiessen W, *et al*. Medical management of pulmonary actinomycosis: data from 49 consecutive cases. J Antimicrob Chemother 2009; 63(4): 839-41.
18. Dujneungkunakorn T, Riantawan P, Tungsagunwattana S. Pulmonary actinomycosis: a study of 16 cases from Central Chest Hospital. J Med Assoc Thai 1999; 82(6): 531-5.

Subclavian Artery Aneurysm Mimicking a Lung Mass: A Case Report and Literature Review

Yu-Ting Lin[1], Shan-Yao Yang[2], I-Ming Chen[3,4], Chia-I Shen[1,4,5]

Subclavian artery aneurysm is a rare vascular disorder that can mimic lung masses in imaging studies, often leading to diagnostic challenges. We reported the case of a 70-year-old man who presented with hemoptysis and progressive left-side chest pain. Initial imaging without contrast suggested a left upper lobe lung mass with mediastinal invasion. Despite multiple diagnostic attempts, no malignancy was identified. Further evaluation with Doppler ultrasound and contrast-enhanced computed tomography revealed a left subclavian artery aneurysm, with a characteristic "yin-yang" sign detected by the Doppler ultrasound. The patient underwent successful endovascular stent placement and showed clinical improvement. In this case report, we reviewed the possible presentation, diagnostic approach, and management strategies of this rare disease. We also highlighted how multi-modality imaging techniques—such as ultrasonography—can offer enhanced diagnostic value. ***(Thorac Med 2025; 40: 222-228)***

Key words: Subclavian artery aneurysm, yin-yang sign

Introduction

Subclavian artery aneurysms are an uncommon subtype of arterial aneurysms [1]. They are more frequently diagnosed in older males and may arise from various causes, including atherosclerosis, trauma, or infection [2-3]. Subclavian artery aneurysms can mimic thoracic malignancies clinically and radiologically, particularly when appearing as mass-like lesions on chest radiographs or computed tomography (CT) scans. Here, we report the case of a subclavian artery aneurysm initially mistaken for a lung malignancy. The case highlights the importance of considering vascular anomalies in the differential diagnosis of mediastinal or pulmonary masses and emphasizes the role of multimodal imaging in an accurate diagnosis and management.

[1]Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. [2]Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan. [3]Division of Cardiovascular Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan. [4]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan. [5]Institute of Clinical Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.
Address reprint requests to: Dr. Chia-I Shen, Department of Chest Medicine, Taipei Veterans General Hospital, No. 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan.

Case Presentation

A 70-year-old man presented to our emergency department with hemoptysis lasting for 3 days. He had underlying diseases with essential hypertension, type 2 diabetes mellitus, and stage 3 chronic kidney disease. During the previous week, he had also experienced left-side back pain, loss of appetite, and exertional dyspnea.

At triage, his vital signs were as follows: body temperature of 37.7°C, blood pressure of 167/77 mmHg, heart rate of 106 beats per minute, and respiratory rate of 22 breaths per minute. Physical examination revealed a generally ill appearance, but no abnormal breathing sounds were detected in the bilateral lung fields. Initial laboratory tests showed leukocytosis (15,790/μL, with 94.1% segmented neutrophils) and an elevated C-reactive protein (CRP) level (17.94 mg/dL). Additional findings included elevated creatinine (2.07 mg/dL) and hyponatremia (130 mmol/L).

Chest X-ray revealed an opacity at the left upper lobe (LUL) adjacent to the mediastinum, with a blunted left costophrenic angle (Fig. 1a). Subsequent chest CT, without contrast enhancement due to concerns about renal function, revealed an LUL mass encasing the left subclavian artery and aortic arch, with invasion to the mediastinum. Left paratracheal mediastinal lymphadenopathy, bilateral bronchiectasis with peribronchial infiltration and left-sided pleural effusion were also revealed (Fig. 2). Under the impression of lung cancer or lung abscess, the patient was admitted to the chest medicine ward for further evaluation.

Empirical antibiotic therapy with ceftriaxone was administrated initially. Despite the treatment, the patient continued to experience low-grade fever and persistent chest and back pain. Endobronchial ultrasound with transbron-

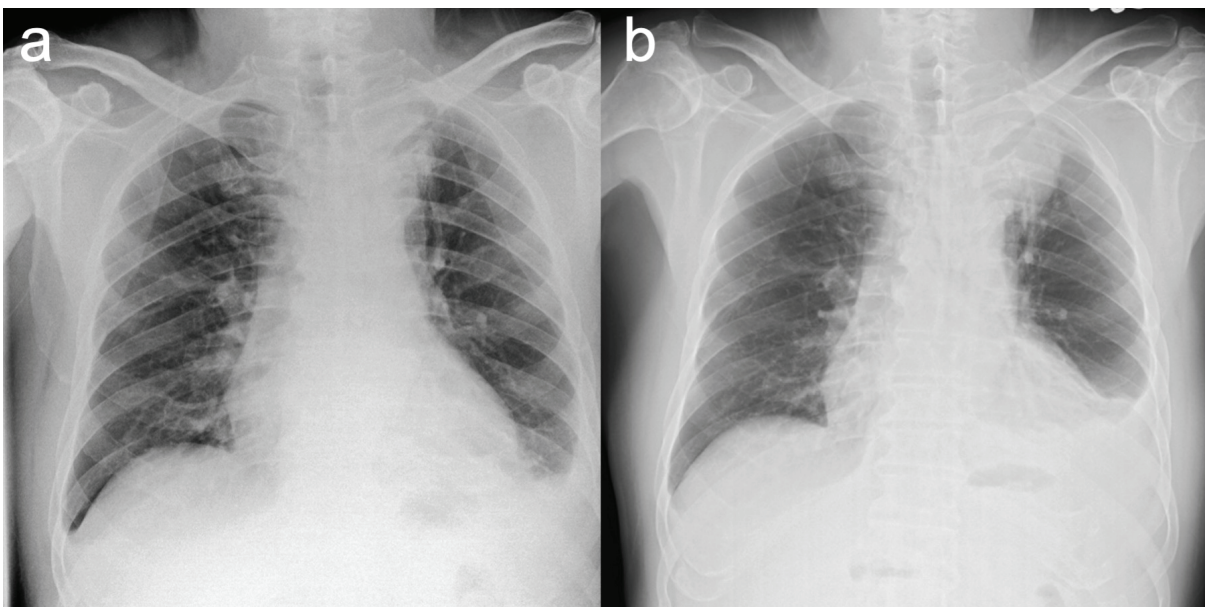


Fig. 1. Chest X-ray performed at the emergency department (a) and 2 weeks after antibiotics treatment (b), showing an enlarging mass at the apex of the left upper lobe.

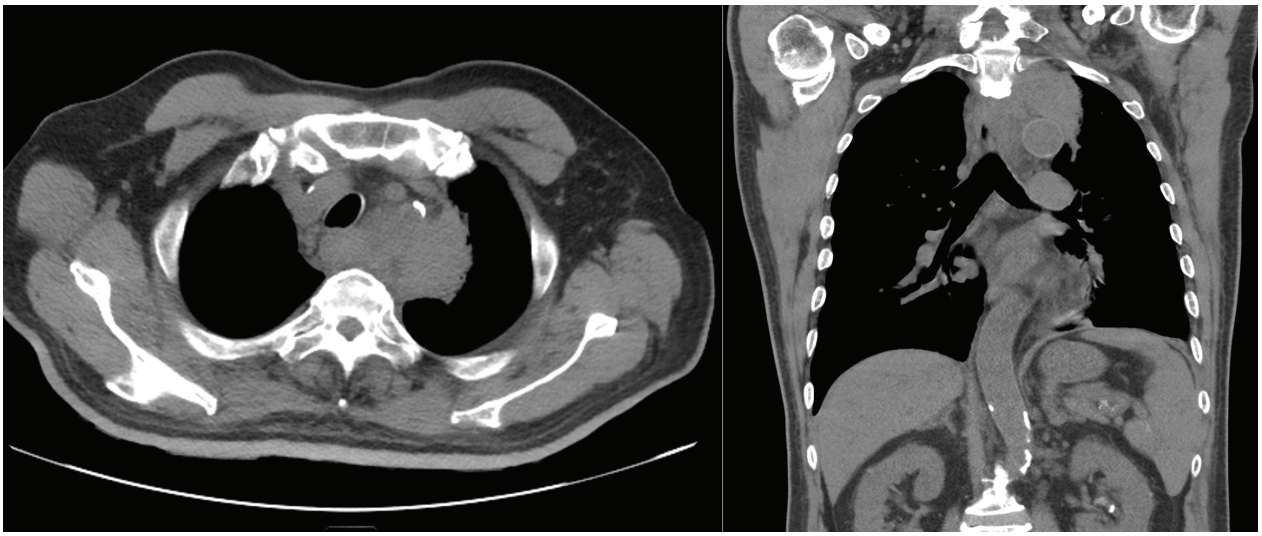


Fig. 2. A left upper lobe mass-like lesion as seen on the non-contrast chest computed tomography at the emergency department.

chial needle aspiration (EBUS-TBNA) was performed to biopsy the LUL mass and lymph nodes at station 7. The pathological finding of the mass revealed necrotizing inflammation, and cultures yielded Streptococcus mitis and Streptococcus oralis. Recurrent fever peaking at 38.9°C was noted 1 day after the procedure, but it resolved promptly after escalation of the antibiotic to levofloxacin. No hemoptysis, increased oxygen requirement, or other life-threatening complications occurred after the procedure. We also attempted a bronchoscopic approach guided by radial probe EBUS. Mild hemoptysis with blood-tinged sputum was observed after the procedure, and was successfully controlled with inhaled epinephrine. The sputum color turned brownish the next day. No other complication was noted. However, the radial probe EBUS-guided bronchoscopic biopsy result was still not diagnostic.

After 2 weeks of antibiotics treatment, serial chest X-rays showed progressive enlargement of the LUL opacity accompanied by intermittent chest tightness (Fig. 1b). Chest ultrasound revealed a hypoechoic, mass-like lesion at the left first intercostal space of the midclavicular line, which appeared to be attached to the chest wall. Color Doppler imaging identified a bidirectional flow overlying the so-called hypoechoic mass. The to-and-fro flow pattern was suggestive of the "yin-yang" sign (Fig. 3). Chest CT with contrast enhancement further confirmed the presence of an aneurysm with wall thickening in the left apical lung, likely arising from the left subclavian artery (Fig. 4).

A cardiovascular surgeon was consulted, and stent placement was performed at the left subclavian artery. The intraoperative finding confirmed a left subclavian artery aneurysm with a maximum diameter of 7 cm. Antibiotic therapy was continued for 4 weeks postoperatively due to suspected infection of the aneurysm. Follow-up imaging showed regression of the aneurysm and improvement in the patient's clinical condition.

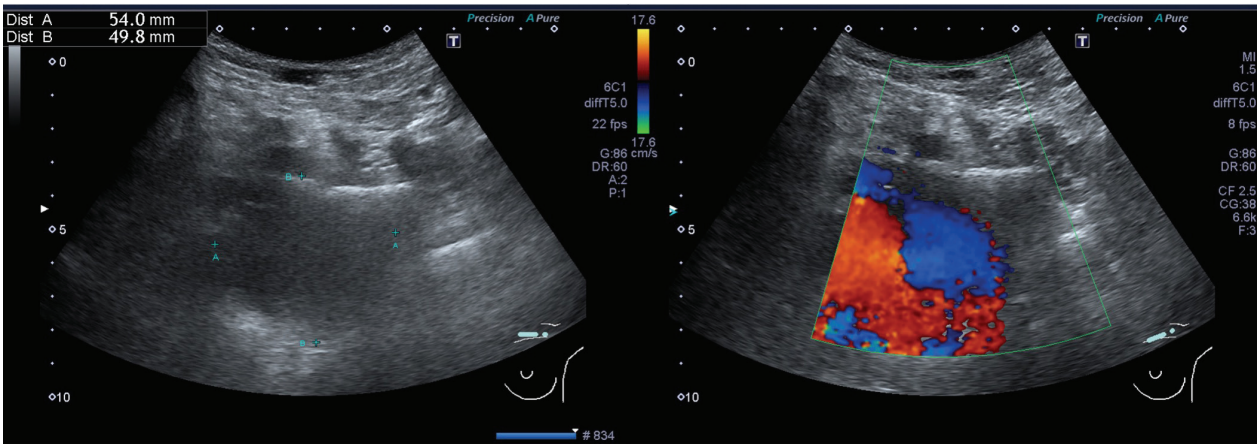


Fig. 3. A to-and-fro color Doppler flow pattern was identified within the hypoechoic mass at the left upper lobe, suggestive of the "yin-yang" sign.

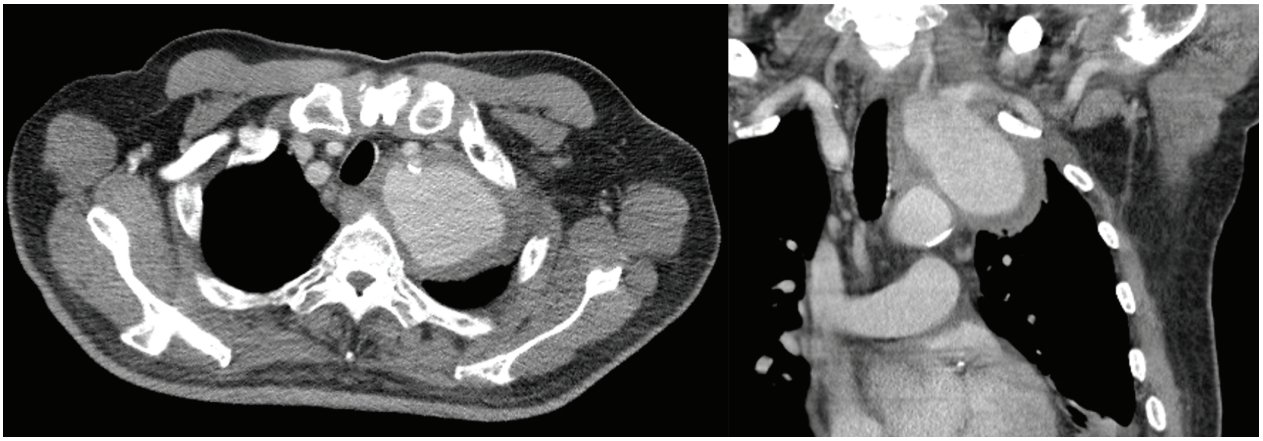


Fig. 4. Contrast-enhanced computed tomography revealed an aneurysm with wall thickening at the left apical lung, likely arising from the subclavian artery.

Discussion

Subclavian artery aneurysm is a rare vascular disease, accounting for 0.13 to 0.5% of all arterial aneurysms [1]. It is more frequently observed in males, and the mean age at diagnosis ranges from 50 to 70 years [2, 3] The etiology of subclavian artery aneurysm is diverse. Infections such as syphilis, bacteria or tuberculosis were the primary causes described in early publications. More recently, thoracic outlet syndrome (TOS), atherosclerosis, trauma and iatrogenic injury have been recognized as common causes [3]. Less frequently, subclavian artery aneurysm may be associated with connective tissue disease, malignancy, coarctation of the aorta and congenital abnormalities, as reported in several case studies [4-7].

The symptoms of subclavian artery aneurysm vary widely [3]. Symptoms related to local compression of adjacent structures include chest pain, dyspnea, stridor, dysphagia, and hoarseness [8, 9]. Neurological symptoms, such as painful upper extremities or sensory deficits,

are also common presentations of a local compressive effect on the brachial plexus [10]. Rupture of the aneurysm may lead to hemoptysis, hemothorax or mediastinal hematoma, which can be life-threatening [11-12]. Thrombosis or embolism, often associated with TOS, can result in limb ischemia [13]. Constitutional symptoms and persistent bacteremia may occur if the aneurysm is infectious in nature [14]. However, some patients remain asymptomatic throughout the entire course of the disease [15].

Diagnosis of subclavian artery aneurysms can be challenging, as their mass-like appearance may lead to a misdiagnosis of thyroid goiter, cervical cyst or neoplasm [15-16]. Given the rarity of this disease, it is often overlooked in initial evaluations. Chest radiographs typically reveal a right upper lobe or a LUL mass lesion, abutting the mediastinum or adhering to the apical chest wall. However, it can be difficult to distinguish a subclavian artery aneurysm from an apical neoplasm based on chest radiographs alone. Ultrasounds can play a valuable role in differentiating vascular from non-vascular lesions. Reports of ultrasonographic diagnosis are rare. Our case presented a "to-and-fro" pattern, also known as a "yin-yang sign", which is a characteristic diagnostic feature of an aneurysm. Under a B-mode scan, aneurysms and pseudoaneurysms appear as fusiform or saccular structures. When pulsed-wave Doppler is used to scan the aneurysm, a "to-and-fro" pattern is observed [17]. The bidirectional flow appears as 2 different colors under color Doppler imaging [18-19].

Among the available imaging modalities, contrast-enhanced CT or angiography remains the most important one, offering high diagnostic accuracy and detailed vascular visualization [20-21]. A multi-modality imaging approach is crucial in evaluating a lung field mass, as it reduces the risk of misdiagnosis, prevents unnecessary interventions, and ensures timely and appropriate treatment.

The treatment of subclavian artery aneurysm is directed toward preventing complications such as limb thrombosis or aneurysm rupture [22-23]. The risk of these complications depends on the location and etiology of the aneurysm. Conservative management with regular follow-up imaging to monitor changes in size or the development of symptoms may be appropriate for patients with small and asymptomatic aneurysms [2]. In contrast, large, rapidly growing, symptomatic, or infected aneurysms often require treatment, as they may result in severe complications and even death [2, 24-25]. Traditional surgical intervention, including thoracotomy or sternotomy with different incision sites, was commonly performed in earlier cases. However, studies suggest that open surgery is associated with longer operation time, postoperative ventilator use, a higher incidence of pulmonary complications, and increased rates of recurrent laryngeal nerve injury and shoulder instability [3, 26].

Since the mid-1990s, endovascular subclavian aneurysm repair has gained popularity and showed favorable outcomes with few complications [27-28]. The most common complications of endovascular treatment are false aneurysm, late thrombosis and in-stent stenosis. Severe complications such as stroke have also been reported [3, 29]. Generally, surgical interventions offer better long-term patency and are preferred for larger aneurysms. In contrast, endovascular treatments are less invasive and are associated with quicker recovery [26, 30].

Conclusion

Subclavian artery aneurysm is a rare disease, and its prognosis largely depends on early detection and appropriate intervention. Clinical physicians should be aware of upper lobe lung opacity with progressive enlargement. Integrating multiple imaging techniques, including chest radiographs, ultrasound, and contrast-enhanced CT, enhances diagnostic precision and helps clinicians optimize patient management.

References

1. Dougherty MJ, Calligaro KD, Savarese RP, *et al*. Atherosclerotic aneurysm of the intrathoracic subclavian artery: a case report and review of the literature. J Vasc Surg 1995; 21(3): 521-9.
2. Brownstein AJ, Rajaee S, Erben Y, *et al*. Natural history of aneurysmal aortic arch branch vessels in a single tertiary referral center. J Vasc Surg 2018; 68(6): 1631-1639 e1.
3. Vierhout BP, Zeebregts CJ, van den Dungen JJ, *et al*. Changing profiles of diagnostic and treatment options in subclavian artery aneurysms. Eur J Vasc Endovasc Surg 2010; 40(1): 27-34.
4. Arikan AA, Omay O, Cakir O, *et al*. A pseudocoarctation of the aorta with a left subclavian artery aneurysm, a case report and a review of the literature. Vasc Endovascular Surg 2021; 55(8): 889-896.
5. Banning SK, Ur R, Malleis J, *et al*. Extrathoracic subclavian artery aneurysm in a patient with suspected genetic arteriopathy. J Vasc Surg Cases Innov Tech 2021; 7(1): 46-50.
6. Colvine K, Gerber I, McQueen F Clinical image: Takayasu arteritis presenting with subclavian aneurysm. Arthritis Rheum 2006; 54(1): 382.
7. Tatebe S, Asami F, Shinohara H, *et al*. Ruptured aneurysm of the subclavian artery in a patient with von Recklinghausen's disease. Circ J 2005; 69(4): 503-6.
8. Takagi H, Mori Y, Umeda Y, *et al*. Proximal left subclavian artery aneurysm presenting hemoptysis, hoarseness, and diplopia: repair through partial cardiopulmonary bypass and perfusion of the left common carotid artery. Ann Vasc Surg 2003; 17(4): 461-3.
9. Windfuhr JP, Schubert D, Remmert S. [Aneurysm of the subclavian artery. An unusual cause of dysphagia] [article in German]. HNO 2004; 52(12): 1097-102.
10. Pfammatter T, Kunzli A, Hilfiker PR, *et al*. Relief of subclavian venous and brachial plexus compression syndrome caused by traumatic subclavian artery aneurysm by means of transluminal stent-grafting. J Trauma 1998; 45(5): 972-4.
11. Ramtoola MT, Bhatti M, Shetty R. A case report of a ruptured subclavian artery aneurysm presenting to the emergency department. Clin Case Rep 2019; 7(4): 797-800.
12. Saliou C, Badia P, Duteille F, *et al*. Mycotic aneurysm of the left subclavian artery presented with hemoptysis in an immunosuppressed man: case report and review of literature. J Vasc Surg 1995; 21(4): 697-702.
13. Archie MM, Gelabert HA. Endovascular reconstruction of subclavian artery aneurysms in patients with arterial thoracic outlet syndrome. Ann Vasc Surg 2019; 57: 10-15.
14. Fatula L, Fleming T, Jones B, *et al*. Mycotic right subclavian artery aneurysm: a rare and challenging pathology. J Vasc Surg Cases Innov Tech 2020; 6(4): 547-549.
15. Beissert M, Jenett M, Trusen A, *et al*. Asymptomatic aneurysm of the proximal right subclavian artery: a rare ultrasound diagnosis. Eur Radiol 2000; 10(3): 459-61.
16. Sinzobahamvya N, Chinyanga HM, Clarke NJ, *et al*. Misdiagnosis of aneurysms: a case report. Cent Afr J Med 1990; 36(9): 230-3.
17. Mahmoud MZ, Al-Saadi M, Abuderman A, *et al*. "To-and-fro" waveform in the diagnosis of arterial pseudoaneurysms. World J Radiol 2015; 7(5):89-99.
18. Caserta MP, Dyer RB. The yin-yang sign. Abdom Imaging 2015; 40(6): 2060-1.
19. Corvino A, Catalano O, de Magistris G, *et al*. Usefulness of Doppler techniques in the diagnosis of peripheral iatrogenic pseudoaneurysms secondary to minimally invasive interventional and surgical procedures: imaging findings and diagnostic performance study. J Ultrasound 2020; 23(4): 563-573.
20. Iino M, Kuribayashi S, Imakita S, *et al*. Sensitivity

and specificity of CT in the diagnosis of inflammatory abdominal aortic aneurysms. J Comput Assist Tomogr 2002; 26(6): 1006-12.

21. Jones CS, Verde F, Johnson PT, *et al*. Nontraumatic subclavian artery abnormalities: spectrum of MDCT findings. AJR Am J Roentgenol 2016; 207(2): 434-41.
22. Li L, Zhang J, Wang R, *et al*. Endovascular repair of a right subclavian artery aneurysm with coil embolization and stent graft: case report and literature review. Ann Vasc Surg 2016; 36: 290 e1-290 e5.
23. Savlania A, Jain P, Thakur UK, *et al*. Extra-thoracic rupture of giant subclavian artery aneurysm. Eur J Cardiothorac Surg 2021; 59(3): 714-716.
24. Boundy K, Bignold LP. Syphilitic aneurysm of the right subclavian artery presenting with hemoptysis. Aust N Z J Med 1987; 17(5): 533-5.
25. Jalaie H, Grommes J, Sailer A, *et al*. Treatment of symptomatic aberrant subclavian arteries. Eur J Vasc Endovasc Surg 2014; 48(5): 521-6.
26. Gu Y, Zhang K, Zhou Z, *et al*. Surgical outcome of proximal isolated subclavian artery aneurysms: a single-center retrospective observational study. J Endovasc Ther 2023; 15266028231210221.
27. Ackroyd R, Singh S, Beard JD, *et al*. Simultaneous brachial embolectomy and endoluminal stenting of a subclavian artery aneurysm. Eur J Vasc Endovasc Surg 1995; 10(2): 248-9.
28. May J, White G, Waugh R, *et al*. Transluminal placement of a prosthetic graft-stent device for treatment of subclavian artery aneurysm. J Vasc Surg 1993; 18(6): 1056-9.
29. Maskanakis A, Patelis N, Moris D, *et al*. Stenting of subclavian artery true and false aneurysms: a systematic review. Ann Vasc Surg 2018; 47: 291-304.
30. Pantoja JL, Rigberg DA, Gelabert HA. The evolving role of endovascular therapy in the management of arterial thoracic outlet syndrome. J Vasc Surg 2022; 75(3): 968-975 e1.

Lethal Complication of Post-air-way Stenting to Trachea and Left Main Bronchus: A Case Report

Kuan-sun Lin[1], Tsai-Wang Huang[1]

Insertion of a metallic airway stent is a valuable method for the treatment of benign and malignant airway stenosis and a tracheal-esophageal fistula. Although stenting for airway stenosis has become widely used, with favorable outcomes, several complications after stenting, such as migration, a tendency for stent fracture, and ingrowth of the tumor or granulation tissue in the stent have occurred. Very few of these reports have described the complications of post-stenting pneumothorax. We report the case of a patient diagnosed with squamous cell carcinoma of the esophagus, complicated by a tracheal-esophageal fistula and treated with a tracheal stent or bronchial stent, who developed post-stenting pneumothorax. Esophageal cancer led to the lethal complication of the tracheal-esophageal fistula, which was complicated in handling. Although tracheal and left main bronchial airway stent placement remains a high risk, careful selection of stents (Y-stents) and placement location can reduce postoperative fatal complications. ***(Thorac Med 2025; 40: 229-232)***

Key words: airway stent, complication, pneumothorax, squamous cell carcinoma of the esophagus

Introduction

Insertion of a metallic airway stent is a valuable method for the treatment of benign and malignant airway stenosis [1]. Although stenting for airway stenosis has become widely popular, with favorable outcomes [2], several complications after stenting, such as migration, a tendency for stent fracture, and ingrowth of a tumor or granulation tissue in the stent could occur [3]. Very few of these reports have described the complications of post-stenting pneumothorax. We report the case of a patient diagnosed with squamous cell carcinoma of the esophagus, complicated by a tracheal-esophageal fistula and treated with a tracheal stent or bronchial stent, who developed post-stenting pneumothorax.

Case Report

A 44-year-old man had a poor appetite, cough, and increased sputum production for 5 to 6 months. Because of acute hypoxic re-

[1]Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China.
Address reprint requests to: Dr. Tsai-Wang Huang, Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital 325, Cheng-Kung Road, 2nd section, Taipei 114, Taiwan, Republic of China.

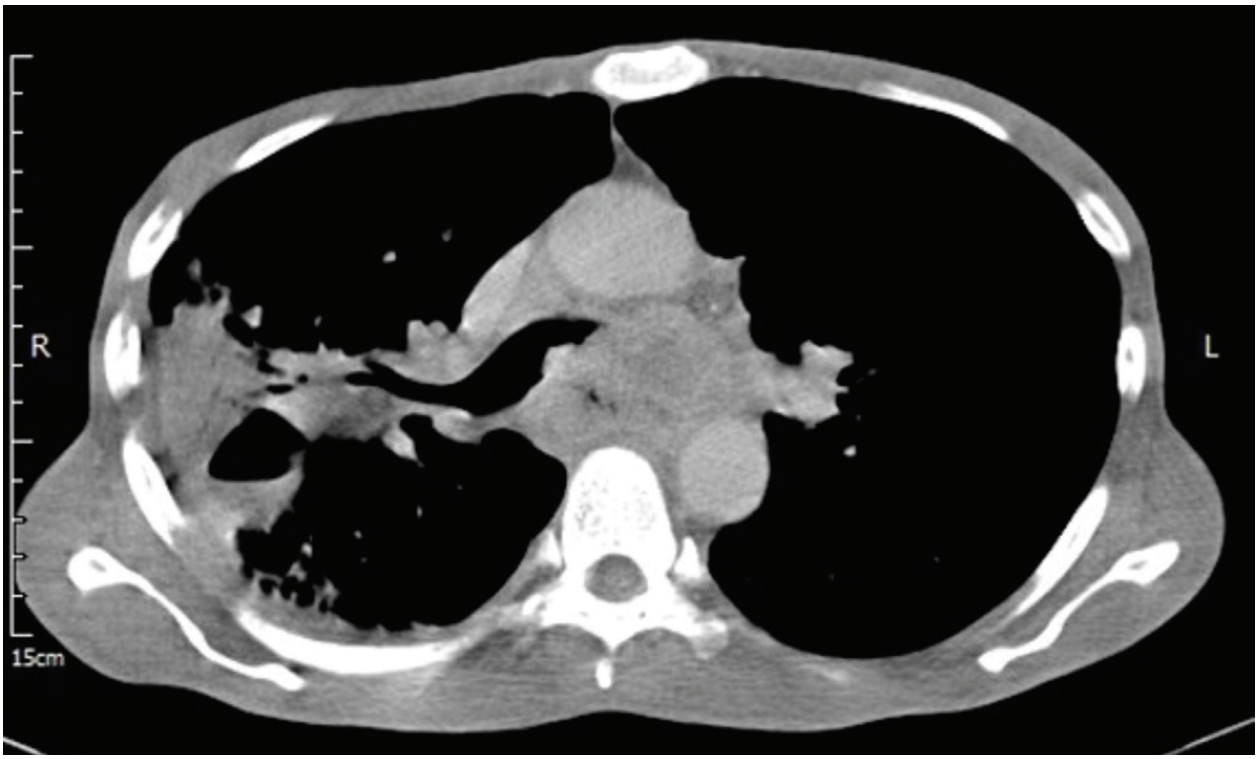


Fig. 1. Chest computed tomography (CT) showed suspected esophageal cancer with a broncho-esophageal fistula and total obstruction of the left main bronchus.

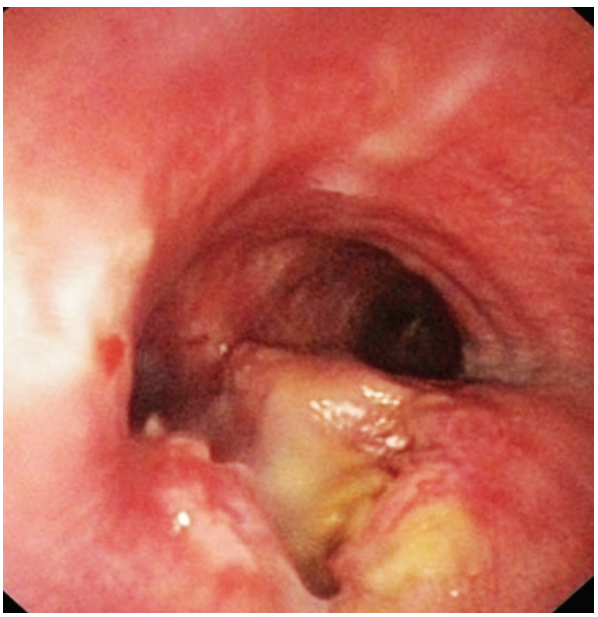


Fig. 2. Mass lesion and perforation located in the left supra-carinal region.

spiratory failure, endotracheal intubation was performed. Based on chest computed tomography (CT) findings, esophageal cancer with a broncho-esophageal fistula and total obstruction of the left main bronchus were suspected (Fig. 1). Bronchoscopy showed a mass lesion and perforation located at the left supra-carinal region (Fig. 2). Upper gastrointestinal (GI) panendoscopy showed a circumferential mass with ulceration, lumen narrowing and whitish coating, 20 to 30 cm from the incisors. The pathology results showed squamous cell carcinoma, moderately to poorly differentiated. Immunohistochemical stains were positive for CK14 and P16 and showed overexpression of P53 and an increased proliferative index of Ki-67. Stenting of the trachea, left bronchus, and esophagus were performed. However, post-

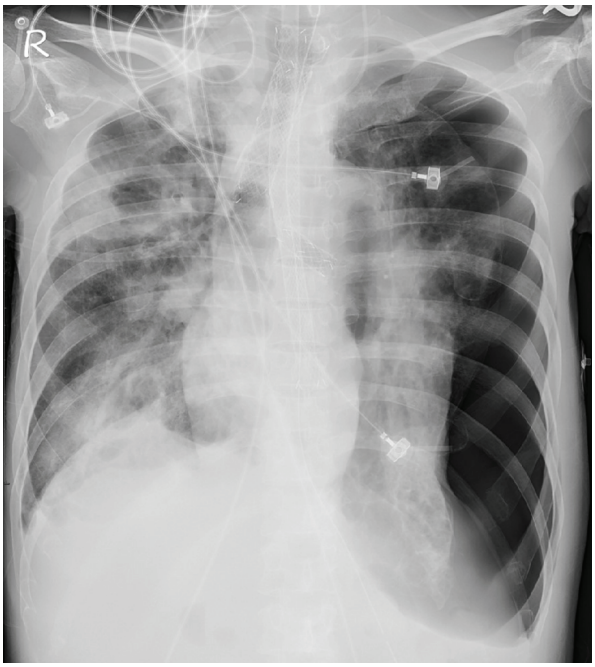


Fig. 3. Post-stenting pneumothorax, left side.

stenting pneumothorax on the left side with desaturation was observed (Fig. 3). Emergency tube thoracostomy on the left side was arranged and full expansion of the lung was noted on the chest radiograph (CXR) after the procedure. Re-expansion pulmonary edema on the left side and bilateral pneumonia with septic shock progressing to acute respiratory distress syndrome (ARDS) were suspected. We continued antibiotics, and prescribed diuretics and inotropic agents. However, the patient died on postoperative day 5.

Discussion

Our study focused on reporting post-airway stenting pneumothorax. The patient was diagnosed with squamous cell carcinoma of the esophagus complicated with a tracheal-esophageal fistula and was treated with a tracheal stent or a bronchial stent.

The first usage of an endotracheal metallic stent in the treatment of stenosis of the trachea was described by Harkins in 1952 [4]. There are several advantages to using the endotracheal metallic stent, including ease of placement via flexible bronchoscopy, low migration rate, and generation of a sufficient force to maintain patency of the strictured region of the airway [5]. However, several complications after stenting have been reported, such as stent fracture, ingrowth of the tumor or granulation tissue in the stent, and airway wall perforation [7]. Tension pneumothorax has been described as an immediate complication of stent placement [3, 7-8].

The symptoms of pneumothorax, mediastinal emphysema and subcutaneous emphysema often appear early after airway stenting. Pneumothorax occurs only if the pleural space is damaged and air accumulates there [9-10].

Conventional CXR is a good tool to use in the diagnosis of pneumothorax, mediastinal emphysema, and subcutaneous emphysema. Bronchoscopy is indicated for visually detecting stent location and injury to the airway. The role of CT in the diagnosis of pneumothorax is controversial. CT is occasionally necessary in some cases of non-detectable mediastinal emphysema or if penetration of mediastinal structures is suspected [9].

Indications for tube thoracostomy are based on clinical symptoms, and radiological and bronchoscopic findings [11]. Small tears (about 1 cm in length) in the absence of a gross air leak and minimal mediastinal and/or subcutaneous emphysema can be treated conservatively, with continuous airway humidification, broad-spectrum antibiotics, and chest physiotherapy [6-7, 10-11]. Lesions longer than 2 cm, with the presence of extensive subcutaneous and/or mediastinal emphysema and pneumothorax,

are indications for early surgical repair [7, 10-11]. In our patient, who was diagnosed as having squamous cell carcinoma of the esophagus complicated with a tracheal-esophageal fistula and treated with tracheal stent or bronchial stent, postoperative CXR showed left-sided pneumothorax. Bronchoscopy showed the stents were without displacement and the airway was intact. Tube thoracostomy was performed and the chest tube was safely removed without air leakage. Subsequent CXRs showed no pneumothorax.

Esophageal cancer led to the lethal complication of the tracheal-esophageal fistula, the handling of which was complicated. Although tracheal and left main bronchial airway stent placement remains a high risk, careful selection of stents (Y-stents) and placement location can reduce fatal postoperative complications.

We suggest that patients diagnosed with squamous cell carcinoma of the esophagus, complicated by a tracheal-esophageal fistula, and treated with a tracheal stent or left bronchial stent have a risk of pneumothorax and potential tension pneumothorax. Careful review of the postoperative CXR is indicated.

Acknowledgements

This study was approved by the institutional review board of our hospital (TSGHIRB 2-104-05-123).

The study was supported in part by a grant from the Foundation for Medical Research of Tri-Service General Hospital (TSGH-C105-178).

References

1. Nouraei SM, Pillay T, Hilton CJ. Emergency management of aorto-bronchial fistula after implantation of a self-expanding bronchial stent. Eur J Cardiothorac Surg 2001; 20(3): 642-4.
2. Saad CP, Murthy S, Krizmanich G, *et al*. Self-expandable metallic airway stents and flexible bronchoscopy: long-term outcomes analysis. Chest 2003; 124(5): 1993-9.
3. Davis N, Madden BP, Sheth A, *et al*. Airway management of patients with tracheobronchial stents. Br J Anaesth 2006; 96(1): 132-5.
4. Harkins WB. An endotracheal metallic prosthesis in the treatment of stenosis of the trachea. Ann Otol Rhinol Laryngol 1952; 61: 932-5.
5. Asano F, Aoe M, Ohsaki Y, *et al*. Deaths and complications associated with respiratory endoscopy: a survey by the Japan Society for Respiratory Endoscopy in 2010. Respirology 2012; 17(3): 478-85.
6. Lemaire A, Burfeind WR, Toloza E, *et al*. Outcomes of tracheobronchial stents in patients with malignant airway disease. Ann Thorac Surg 2005; 80(2): 434-7; discussion 437-8.
7. Conacher ID. Instrumental bronchial tears. Anaesthesia 1992; 47(7): 589-90.
8. Matsuda N, Matsumoto S, Nishimura T, *et al*. Perioperative management for placement of tracheobronchial stents. J Anesth 2006; 20(2): 113-7.
9. Hofmann HS, Rettig G, Radke J, *et al*. Iatrogenic ruptures of the tracheobronchial tree. Eur J Cardiothorac Surg 2002; 21(4): 649-52.
10. Kaloud H, Smolle-Juettner FM, Prause G, *et al*. Iatrogenic ruptures of the tracheobronchial tree. Chest 1997; 112(3): 774-8.
11. Jougon J, Ballester M, Choukroun E. *et al*. Conservative treatment for postintubation tracheobronchial rupture. Ann Thorac Surg 2000; 69(1): 216-20.

Pulmonary Cryptococcosis Coexisting with Metastatic Pulmonary Tumors: A Case Report

Chen-Chuan Hsu[1], Chiung-Hsin Chang[1], Tai-Di Chen[2], Yu-Hsiu Chen[2], Jia-Shiuan Ju[1], How-Wen Ko[1]

Pulmonary cryptococcosis (PC) is a common disease caused by *Cryptococcus neoformans* infection. Differentiating PC from pulmonary malignancy in the setting of multiple pulmonary lesions can be challenging. We reported a patient with biopsy-proven PC and metastatic pulmonary tumors, and discuss the clinical reasoning behind the managing of multiple pulmonary nodules. ***(Thorac Med 2025; 40: 233-238)***

Key words: pulmonary cryptococcosis, lung metastasis, treatment response, multiple pulmonary nodules

Introduction

Pulmonary cryptococcosis (PC) is the pulmonary manifestation of *Cryptococcus neoformans* infection after inhalation of its basidiospore. Systemic cryptococcosis can then develop through the bloodstream and involve multiorgan systems, including the central nervous system (CNS), and mucocutaneous and musculoskeletal systems. The diverse clinical spectrum of PC, ranging from asymptomatic colonization to pneumonitis causing respiratory failure, depends on the exposure burden, virulence factor of the inhaled strain and host immunity [1]. The diagnosis of PC relies on image evaluation, antigen detection, culture evidence, or a proved histologic specimen [1]. To date, fluconazole is the first-line treatment for PC [2].

Distinguishing PC from pulmonary malignancy can be challenging due to the nonspecific symptoms, varied radiographic presentations and uncertain correlation of serum cryptococcal antigen detection [1]. Several case reports have highlighted the diagnostic complexity of PC, which can mimic lung mass [3]. However, few reports have described the co-diagnosis of PC and pulmonary malignancy [4]. Hence, we report the case of a patient with multiple pulmonary lesions that were ultimately diagnosed as PC and lung metastases by lung biopsy.

Case Report

We present the case of a 63-year-old male

[1]Department of Thoracic Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan. [2]Department of Anatomic Pathology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.
Address reprint requests to: Dr. How-Wen Ko, Department of Thoracic Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan No. 5, Fuxing St., Guishan Dist., Taoyuan, Taiwan.

with underlying type 2 diabetes mellitus, hypertension, chronic kidney disease and early-stage oral cancer, for which he underwent total tumor excision several years ago. He previously worked in the rubber industry and had a history of smoking (50 pack-years) and daily alcohol consumption, specifically 1 bottle of Gaoliang liquor per day. At the beginning, he suffered from left-lower quadrant abdominal pain with referred pain to the left lower back. He underwent colonoscopy, which revealed a polypoid tumor at the ascending colon. He then received a scheduled right hemicolectomy for suspected colon cancer. The pre-operative computed tomography (CT) scan showed a 2 cm mass in the ascending colon, abdominal lymphadenopathy, pancreatic tail atrophy with a dilated pancreatic duct and multiple lung nodules with patchy opacity at the right upper lobe (RUL) (Fig. 1). The pathology report of the colon tumor revealed tubulovillous adenoma without definite malignant cells. Later, he was referred to the pulmonologist for evaluation of multiple lung lesions. CT-guided percutaneous lung biopsy of the largest accessible right middle lobe (RML) nodule was performed, and the pathology report showed cryptococcosis (Fig. 2). Fluconazole 200 mg per day was prescribed at the outpatient

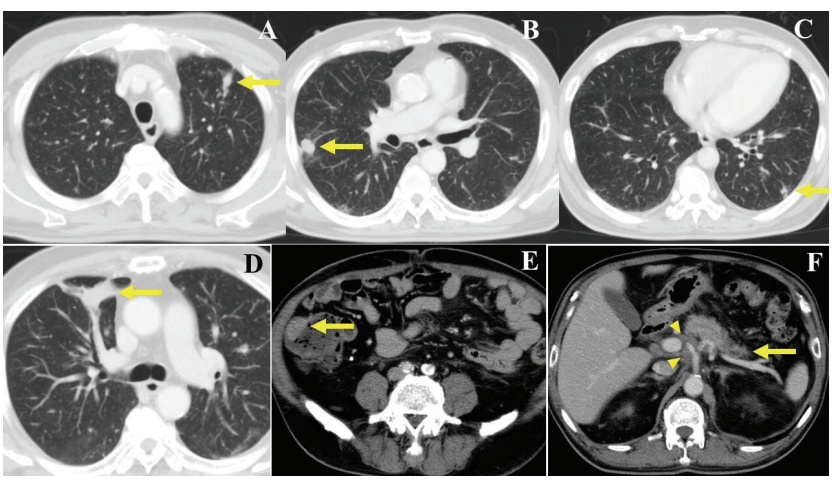


Fig. 1. Initial CT before the treatment. (A-C) Multiple lung nodules of varied sizes at bilateral lungs (arrow) were noted in the chest CT. (D) Patchy opacity consolidation was seen in the right upper lobe (RUL) (arrow). (E) A 2-cm mass is shown at the ascending colon (arrow). (F) Enlarged abdominal lymph nodes (arrowhead), and atrophy of the pancreatic tail with a dilated pancreatic duct (arrow) are seen in the abdominal

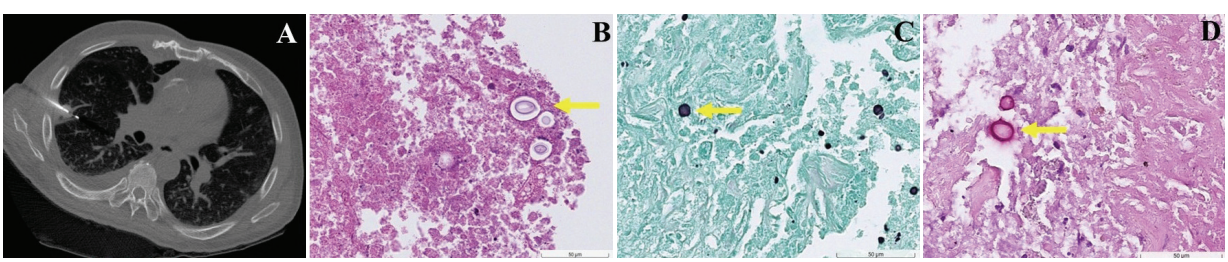


Fig. 2. CT-guided biopsy of the lung nodule in the right middle lobe (RML) before treatment. (A) The CT-guided biopsy was performed at the most accessible nodule in the RML. (B) Histological findings showed some encapsuled pale-grey, round, yeast-form organisms (arrow), which were highlighted by (C) Grocott methenamine silver stains, and (D) Mucicarmine stains. (hematoxylin-eosin stain [B], magnification x400 [B, C, D]).

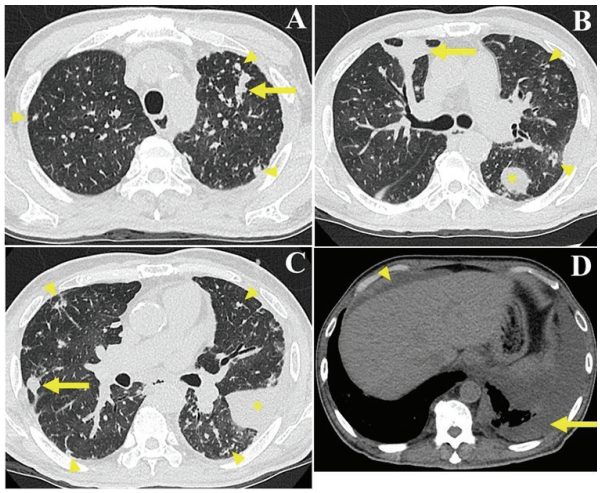


Fig. 3. HRCT follow-up after 3 months of anti-fungal therapy (compared with initial CT images). (A) Enlarged nodule-like lesion (arrow) at the left upper lobe (LUL). (B) Stationary RUL consolidation (arrow). (C) Stationary RML biopsy-proven pulmonary cryptococcosis (arrow). Newly found or enlarging nodules were highlighted (arrowhead) in (A) and (B) and (C). (D) Newly developed left pleural effusion (arrow) and perihepatic ascites (arrowhead). Interlobular effusion was highlighted (asterisk) in (B) and (C).

department (OPD) for the management of pulmonary cryptococcosis.

He had regular follow-up and received fluconazole at the OPD. However, he developed progressive dyspnea with borderline saturation despite 3 months of anti-fungal treatment. The follow-up chest high-resolution computed tomography (HRCT) (Fig. 3) showed the increased extent and numbers of multiple nodules in bilateral lungs, with varied sizes, stationary RUL consolidation, newly developed left pleural effusion and ascites. For a possible alternative diagnosis, endobronchial ultrasound transbronchial biopsy was planned. However, hypoxemic respiratory failure developed before he received bronchoscopy.

He was then intubated with mechanical ventilator (MV) support and admitted to the intensive care unit. Empiric antibiotics, including carbapenem, were initiated. Liposomal amphotericin B was added due to suspected severe PC following the failure of fluconazole treatment. A comprehensive pathogen survey, including tests for legionella, influenza, COVID-19, mycobacteria, aspergillus, *Pneumocystis jirovecii*, cytomegalovirus, and human immunodeficiency virus (HIV) was performed utilizing antigen detection, polymerase chain reaction, sputum culture and bronchoalveolar lavage (BAL) fluid examination, but yielded no specific positive finding. The cryptococcus antigen tests from serum and BAL fluid were both negative. The cytology of BAL fluid was negative.

However, elevated carcinoembryonic antigen and M protein were noted on protein electrophoresis, which shed light on a possible alternative diagnosis. We performed a pleural effusion study and biopsy of the RUL consolidation for suspected PC coexisting with pulmonary malignancy. Cytology of the pleural effusion revealed metastatic adenocarcinoma. CT-guided biopsy from the RUL consolidation suggested adenocarcinoma with a mucinous feature (Fig. 4A-E), and further mutational analysis by AmoyDx® multiplex PCR identified a KRAS G12D/S mutation. Bone marrow biopsy (Fig. 5) was also conducted and indicated multiple myeloma. A whole body CT scan was performed to survey for cancer of unknown origin, and revealed an enlarging mass-like lesion (4.6 cm) at the pancreas tail (Fig. 4F), with suspected peritoneal carcinomatosis. After discussion with the oncologist, the diagnosis of pancreatic cancer with lung metastases was established. Because of the difficulty in MV liberation, the patient received palliative care and the patient's family decided to withdraw MV support for hospice care. The patient passed away 70 days after admission.

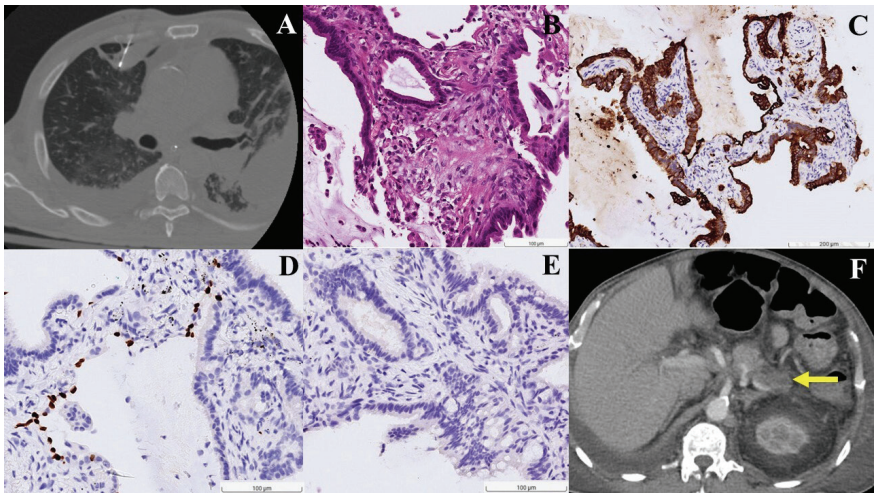


Fig. 4. CT-guided biopsy of the RUL consolidation was performed after admission with mechanical ventilator support. (A) CT-guided re-biopsy was performed at the RUL consolidation. (B) Histological findings revealed adenocarcinoma with mucinous features, and immunohistochemistry study showed (C) positive for CK7 and negative for (D) TTF-1 and (E) p40. (F) CT follow-up 4.5 months after the initial CT showed a 4.6 cm mass at the pancreas tail (arrow). (hematoxylin-eosin stain [B], magnification x200 [B, D, E], x100 [C])

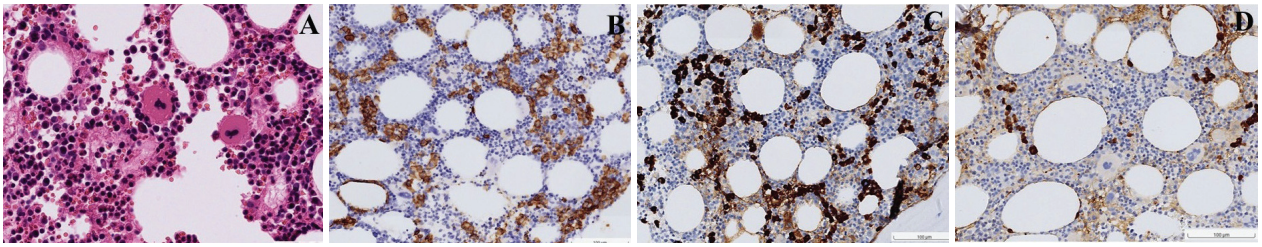


Fig. 5. Bone marrow biopsy indicated multiple myeloma. (A) Interstitial infiltrates of plasma cells, including plasma cells with large nuclei and prominent nucleoli. Immunohistochemistry study showed plasma cells highlighted by (B) CD138 immunostain. (C) Lambda and (D) Kappa immunostains showed lambda light chain restriction in the plasma cells. (hematoxylin-eosin stain [A], magnification x400 [A], x200 [B, C, D])

Discussion

This patient suffered from a case of bilateral multiple lung lesions with pathology-proven PC and lung metastases. Due to the initial pathology-proved diagnosis of PC without malignancy, he received anti-fungal treatment alone. However, his symptoms deteriorated with radiographic progression of bilateral lung lesions and newly developed pleural effusion resulting in respiratory failure. Re-biopsy of another lung lesion confirmed that the malignancy was a coexisting diagnosis, which explained his clinical deterioration despite first-line PC treatment.

Zheng and colleagues [4] described 3 patients who initially presented with multiple lung nodules on imaging, and were then eventually diagnosed with both PC and lung adenocarcinoma by thoracoscopy. In 1 of these cases, the preoperative diagnosis was lung cancer with intrapulmonary metastasis. Another patient was diagnosed with PC by histological examination initially and received fluconazole therapy but later underwent lobectomy due to the poor response of the remaining lesion. The clinical scenario was similar to that of our patient, in-

dicating that close monitoring of the treatment response was essential to address multiple lung nodules.

Pulmonary cryptococcosis can coexist with lung metastasis and cause misleading in the diagnosis of multiple lung nodules. Malignancy itself and impaired immunity from anti-cancer treatment pose a risk to PC development [1]. Unfortunately, discriminating between PC and pulmonary malignancy, whether primary lung cancer or lung metastases, is difficult based on image evaluation alone. Typical PC appears as peripheral clustered nodules on CT imaging [5], but other presentations, including single or multiple nodules, consolidation, cavitation or mass-like lesions, have been reported, especially in immunocompromised patients [1], similar to the diversity of CT imaging characteristics of lung metastases. In addition, extramedullary disease of multiple myeloma, defined as presenting soft tissue plasmacytoma derived from hematogenous spread [6], though rare, can also involve lung parenchyma [7], mimicking lung cancer. Thus, when treating patients with proven PC, synchronous diagnosis of different etiologies of different nodules, particularly malignancy, should be kept in mind.

An unexpected clinical course in a patient receiving PC treatment should include consideration of drug resistance or coexistence of an alternative diagnosis. Fluconazole is first-line treatment with a duration of 6 to 12 months in isolated PC [2]. In severe, isolated PC, liposomal amphotericin B combined with flucytosine or fluconazole is recommended as the initial treatment, similar to the management of cryptococcal meningitis [2]. In a study of non-AIDS patients with histologically proven PC, by Song KD and colleagues [5], all patients achieved either complete or partial response with surgical resection and/or fluconazole therapy. Features included slow progression of lung lesions throughout the months before treatment and persistent nodular lesions on follow-up imaging, with improved symptoms months after fluconazole therapy alone. An early case study of HIV-negative PC patients [8] found an 84% antifungal therapy treatment success rate and 5% 1-year cryptococcosis-related mortality.

Nevertheless, reports of fluconazole-resistant strains of cryptococcus are emerging. A systematic review that analyzed isolates collected from HIV-positive patients with cryptococcosis revealed that the prevalence of fluconazole-resistant strains was 10.6% and 24.1% in incidental and relapse cases, respectively [9]. Persistent cryptococcus infection was defined as positive cerebrospinal fluid cultures after 4 weeks of adequate antifungal treatment [10]. However, cryptococcal antigen levels have shown limited clinical utility in distinguishing clinical responders from non-responders to anti-fungal therapy [11]. Currently, there are no standardized guidelines for the treatment and follow-up of isolated PC without CNS involvement. Therefore, re-evaluation of the treatment response, including imaging, cryptococcus cultures, serum cryptococcus antigen, and re-biopsy, should be considered if clinical and radiologic improvement is not observed after the initial 4-8 weeks of consolidated treatment.

Given the indolent natural course of isolated PC and its slow response to first-line fluconazole treatment, relatively rapid progression of lung lesions should prompt the physician to consider arranging a re-sampling for resistant strain detection and/or re-biopsy for evaluation of a differential diagnosis.

Conclusion

Pulmonary cryptococcosis can coexist with lung metastases. When treating a patient with multiple lung nodules with histologically-proven PC, re-evaluation of persistent PC or an alternative diagnosis should be considered if there is no treatment response following the initial consolidated antifungal therapy.

References

1. Setianingrum F, Rautemaa-Richardson R, Denning DW. Pulmonary cryptococcosis: a review of pathobiology and clinical aspects. Med Mycol 2019; 57(2): 133-150.
2. Chang CC, Harrison TS, Bicanic TA, *et al*. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM. Lancet Infect Dis 2024; 24(8): e495-e512.
3. Allena, N., *et al*., Pulmonary cryptococcosis mimicking lung cancer: a diagnostic challenge. Cureus 2023; 15(10): e47597.
4. Zheng GX, Kolli M, Tale S, *et al*. Clinical characteristics of pulmonary cryptococcosis coexisting with lung adenocarcinoma: three case reports. World J Clin Cases 2020; 8(24) :6444-6449.
5. Song KD, Lee KS, Chung MP, *et al*. Pulmonary cryptococcosis: imaging findings in 23 non-AIDS patients. Korean J Radiol 2010; 11(4): 407-16.
6. Blade J, Beksac M, Caers J, *et al*. Extramedullary disease in multiple myeloma: a systematic literature review. Blood Cancer J 2022; 12(3): 45.
7. Saidi I, Tourane LOEI, Batahar SA, *et al*. A case of multiple myeloma with lung plasmacytoma. Respir Med Case Rep 2022; 39: 101713.
8. Pappas PG, Perfect JR, Cloud GA, *et al*. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis 2001; 33(5): 690-699.
9. Bongomin F, Oldadele RO, Gago S, *et al*. A systematic review of fluconazole resistance in clinical isolates of Cryptococcus species. Mycoses 2018; 61(5): 290-297.
10. Perfect JR, Dismukes WE, Dromer F, *et al*. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010; 50(3): 291-322.
11. Aberg JA, Watson J, Segal M, *et al*. Clinical utility of monitoring serum cryptococcal antigen (sCRAG) titers in patients with AIDS-related cryptococcal disease. HIV Clin Trials 2000; 1(1): 1-6.