ISSN 1023-9855

胸腔醫學

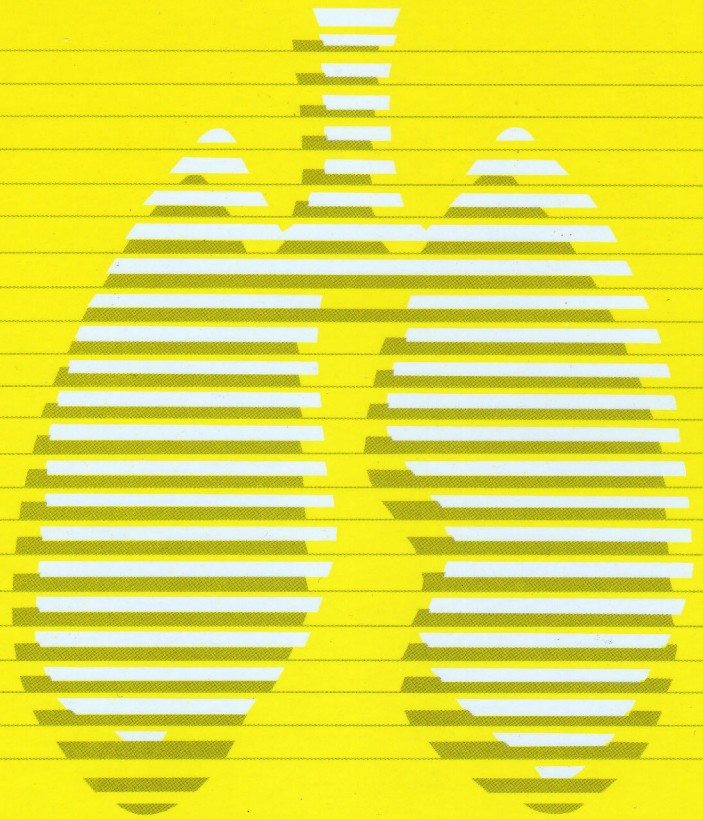
Thoracic Medicine

The Official Journal of Taiwan Society of Pulmonary and Critical Care Medicine

Vol.32 No.3 June 2017

第三十二卷 第三期

中華民國一〇六年六月



台灣胸腔暨重症加護醫學會

10048 台北市常德街 1 號

No. 1, Changde St., Jhongjheng Dist.,

Taipei City 10048, Taiwan

ISSN 1023-9855

中華民國一〇六年六月　第三十二卷　第三期

ISSN 1023－9855

胸腔醫學
Thoracic Medicine

The Official Journal of Taiwan Society of Pulmonary and Critical Care Medicine

Vol.32 No.3 June 2017

原著

病例報告

中華民國一〇六年六月　第三十二卷　第三期

ISSN 1023－9855

Vol.32 No.3 June 2017

胸腔醫學

Thoracic Medicine

The Official Journal of Taiwan Society of Pulmonary and Critical Care Medicine

Orginial Articles

Case Reports

Weekly Hospital-Based Pulmonary Rehabilitation for Chronic Obstructive Airway Disease Maintains Exercise Capacity and Reduces Hospitalization

Chung-Shu Lee*, Fu-Tsai Chung*, Shu-Chuan Ho*,**, Meng-Heng Hsieh*, Yueh-Fu Fang*, Te-Fang Sheng*, Li-Fei Chen*, Wen-Ching Jao*, Horng-Chyuan Lin*

Introduction: This retrospective study aimed to evaluate the effects of a supervised, weekly, hospital-based pulmonary rehabilitation (PR) program on exercise capacity and clinical outcome in patients with chronic obstructive airway diseases (COAD) in a tertiary-care hospital in Taiwan.

Methods: Eighty-four COAD patients were divided into PR (n=42) or non-PR (n=42) groups. Subjects in the PR group regularly took part in a once-a-week rehabilitation program in the hospital for a period of 12 months. Pulmonary function was measured and 6-minute walk tests were given every 3 months. Total duration and time of hospitalization and emergency room (ER) consultation were analyzed.

Results: There was no demographic difference between the 2 groups. During the study period, the 6-minute walk distance increased in the PR group (from 402.5±18.3 to 410.4±17.8 meters), but significantly decreased in the non-PR group (from 430.7±12.8 to 376.0±24.9 meters, $p<0.05$). Forced vital capacity was significantly higher in the PR group at 6 and 12 months, compared to the non-PR group. Hospital admissions and length of stay were significantly decreased in the PR group compared to the non-PR group (0.29±0.55 vs. 0.64±1.02 visits and 1.88±4.16 vs. 6.71±14.82 days, respectively, $p<0.05$). Subjects in the PR group also had a lower rate and duration of ER visits than those in the non-PR group (0.24±0.53 vs. 0.93±1.67 visits and 0.36±0.88 vs. 2.12±4.17 days, respectively, $p<0.05$).

Conclusion: Weekly hospital-based PR can maintain functional exercise capacity and improve pulmonary function in COAD patients. Hospital and ER visits and length of stay were also reduced. ***(Thorac Med 2017; 32: 115-124)***

Key words: hospital-based pulmonary rehabilitation, chronic obstructive airway diseases, exercise capacity, hospitalization, pulmonary function

*Department of Thoracic Medicine, Chang Gung Medical Foundation, Chang Gung University, College of Medicine, Taipei, Taiwan; **School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan
Address reprint requests to: Dr. Horng-Chyuan Lin, Department of Thoracic Medicine, Chang Gung Medical Foundation, Chang Gung University, College of Medicine, 199 Tun Hwa N. Rd., Taipei, Taiwan

Introduction

Pulmonary rehabilitation (PR) is a core component of the management of patients with chronic obstructive airway diseases (COAD), such as asthma, bronchiectasis, and chronic obstructive pulmonary disease (COPD) [1], which are characterized by impaired lung function and limited exercise tolerance due to mucus hypersecretion and respiratory muscle dysfunction [2]. Systemic effects of COAD involve respiratory and skeletal muscles [3-5]. PR helps alleviate symptoms, optimize functional capacity, and reduce the use of healthcare resources for COAD patients [6], but there is still no consensus regarding the optimal program and duration.

Some reports show that the benefits of PR, in terms of functional exercise capacity and quality of life, are maintained for up to 9 months [7-8]. However, the benefits appear to decline by 12 months [2], unless the program is of longer duration [9] or involves ongoing maintenance exercise [10-11]. Recent reviews of PR by the American Thoracic Society (ATS) and European Respiratory Society (ERS) in 2006 [12], and the American College of Chest Physicians (ACCP) in 2007 [13], call attention to the lack of evidence on optimal duration and program. Previous studies found that a 3-month home pulmonary exercise program improves exercise endurance and dyspnea sensation in COAD patients with exercise intolerance [14-15]. Moreover, regular exercise after the initial intensive phase of rehabilitation may be protective against increased dyspnea and perceived limitations in walking, which are characteristics of progressive COAD [16].

This study hypothesized that the benefits of a PR program can be evaluated based on serial measurements of pulmonary function and the 6-minute walk test (6MWT), as well as clinical outcomes like emergency room (ER) consultation and hospitalizations. This study therefore aimed to evaluate the clinical effects of 12-month comprehensive PR that combines a weekly hospital-based PR program with a home exercise program on lung function, exercise tolerance, and clinical outcome in COAD patients.

Patients and Methods

Study design

This longitudinal cohort study followed a group of COAD patients from the day of entering an outpatient rehabilitation program until the end at 12 months. The patients' pulmonary function was measured by spirometry and the 6-minute walk distance (6MWD) test every 12 weeks. The study design was approved by the Institutional Review Board (IRB), Chang Gung Medical Foundation (IRB no. 100-1077B). Methodology and patient confidentiality were also approved by our IRB.

Study subjects

Eighty-four patients with COAD, including COPD, asthma and bronchiectasis, that met the diagnostic criteria of the ATS guidelines [12], were enrolled. They were all regularly followed up at the outpatient department (OPD) during a 12-month period and received weekly hospital-based PR. Inclusion criteria were: (1) patients with regularly scheduled clinical OPD follow-up; (2) exertional dyspnea and exercise intolerance, despite conventional medical therapy; (3) good motivation to take part in a hospital-based PR program; (4) no impairment of the lower extremities; and (5) no other significant systemic problems, such as ischemic heart disease, musculoskeletal disorder, or other disabling disease

that might interfere with the patient's ability to undergo a training program.

Pulmonary rehabilitation program

The patients were divided into 2 groups: a 12-month hospital-based PR group and a control group. The treatment protocol had 4 components: (a) patient education; (b) breathing exercise and lung expansion exercise; (c) bronchial hygiene; and (d) exercise re-conditioning training.

Patient education: All patients received information on the proper use of medication, disease pathophysiology, muscle relaxation, energy conservation and bronchial hygiene methods, coping with acute dyspnea, and exercise guidance.

Breathing exercise and lung expansion exercise: All patients were taught to use pursed-lip/diaphragmatic breathing control during limb muscle exercise training and bronchial hygiene. During each weekly clinical visit, patients underwent expansion therapy with intermittent positive pressure breathing for 20 minutes.

Bronchial hygiene: Postural drainage, breathing exercise, and an effective coughing technique (forced expiratory technique) to improve airway clearance were practiced daily at home and weekly at the hospital by patients with mucus hyper-secretion.

Exercise re-conditioning and exercise training: Different types of physical exercises were used, including paced walking, limb strength training, and ergometer bicycle training. This was a constant work rate exercise with warm-up and cooling down. Participants were instructed to do paced walking under supervision and to walk for 20 min at home twice a day for lower limb training, until they perceived symptoms of breathlessness and muscle fatigue. Upper limb strength was adjusted accordingly, twice a day. The weekly clinic visits involved bicycle ergometer training for 20 minutes.

Clinical assessments

Exercise capacity

Exercise capacity was measured by using the 6MWT. Patients performed this test with a pulse oximeter with a finger transducer (Criticare, Systems Inc) and encouragement from the accompanying therapist. All patients were familiarized with the test before the study.

Pulmonary function

Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC were measured by a trained therapist at the beginning of the study, during each clinical visit every 3 months, and at the end of the PR training period.

Clinical outcomes

Medical records obtained from the same hospital included OPD and ER consultation records and admission history during the study period. Clinical outcome was determined by the number of hospitalizations and length of stay in the wards and/or ER.

Statistical analysis

All data are presented as the mean±SEM. Statistical analysis was performed using Prism for PC. Descriptive analysis was carried out to evaluate the demographic and clinical characteristics of the patients. Unpaired Student's *t* tests were used to compare the 2 groups in terms of walking distance, Borg's scale, FEV_1, and FVC. Repeated measures ANOVA was used to compare data within groups. Statistical significance was defined as $p<0.05$.

Results

Patient characteristics

Baseline characteristics in terms of gender, age, BMI, initial exercise capacity (6MWD), SaO_2, pulmonary function, and Borg scores were not significantly different between the PR and non-PR groups (Table 1).

Pulmonary function

During the 12-month study period, pulmonary function remained steady in the PR group, but declined significantly in the non-PR group. FVC was significantly higher in the PR group than in the non-PR group at 6 months (2.02±0.18 vs. 1.55±0.11 L, $p<0.05$) and 12 months (2.06±0.12 vs. 1.73±0.10 L, $p<0.05$) (Figure 1), and FEV_1 followed the same trend. At 6 months, the PR group had significantly higher FEV_1 than the non-PR group (1.31±0.15 vs. 0.93±0.08 L, $p<0.05$) (Figure 2).

Exercise capacity

During the 12-month study period, the 6MWD was maintained in the PR group, increasing from 402.5±18.3 meters at the initial phase to 410.4±17.8 meters at the end of 12 months of PR (Figure 3). In the non-PR group (control), the 6MWD had significantly decreased (from 430.7±12.8 to 376.0±24.9 meters, $p<0.05$) at 12 months.

Clinical outcomes

Of the 42 patients in the non-PR group, 17 (40.5%) had 39 episodes of acute exacerbation resulting in 39 ER visits with a total stay of 76 days in the ER (Table 2). Eight (19.0%) PR patients had 10 episodes of ER visits, with a total

Table 1. Baseline Characteristics of Both Groups

	PR group (n=42)	Non-PR group (n=42)	*p*
Gender (M/F)	30/12	32/10	NS
Age	62.4 ± 2.2	65.9 ± 1.7	NS
BMI (kg/m^2)	24.3 ± 0.7	24.5 ± 1.1	NS
Smoking			
Never	0	7	NS
Current	30	29	
Ex-	12	6	
Pulmonary function			
FVC (L)	1.92 ± 0.11	1.86 ± 0.89	NS
FEV_1 (L)	1.24 ± 0.09	1.21 ± 0.09	NS
FEV_1/FVC (%)	63.90 ± 2.35	63.22 ± 2.47	NS
6 MWT			
6 MWD (meters)	402.5 ± 18.3	430.7 ± 12.8	NS
SaO_2 (%)	95.3 ± 0.4	94.9 ± 0.5	NS
Borg score	1.1 ± 0.2	1.1 ± 0.2	NS

Data are expressed as mean±SEM

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SaO_2, Saturation; 6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; NS, not significant

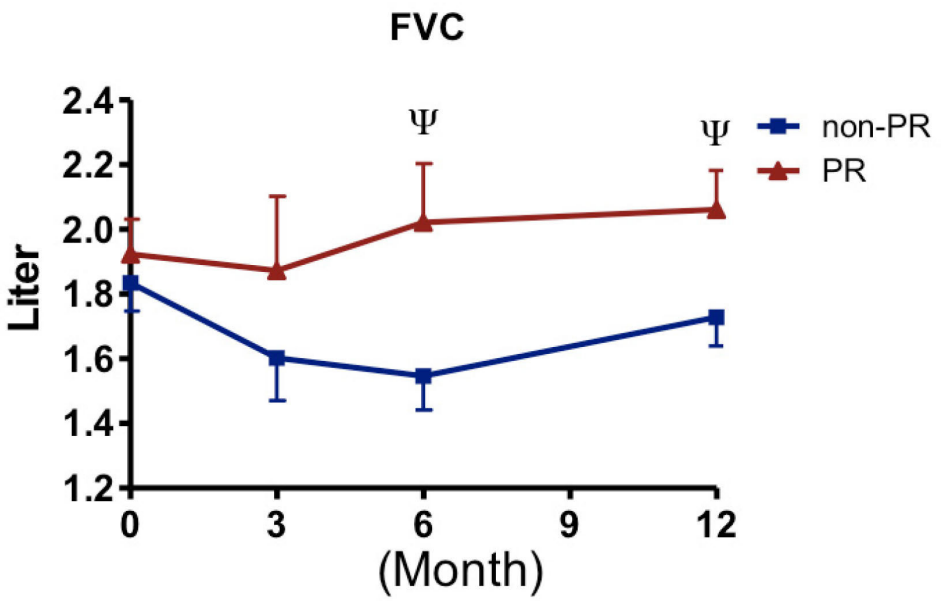


Fig. 1. Forced vital capacity was significantly higher in the PR group at 6 and 12 months of the study period. Ψp<0.05, non-PR 6-month and 12-month FVC vs. PR 6-month and 12-month FVC.

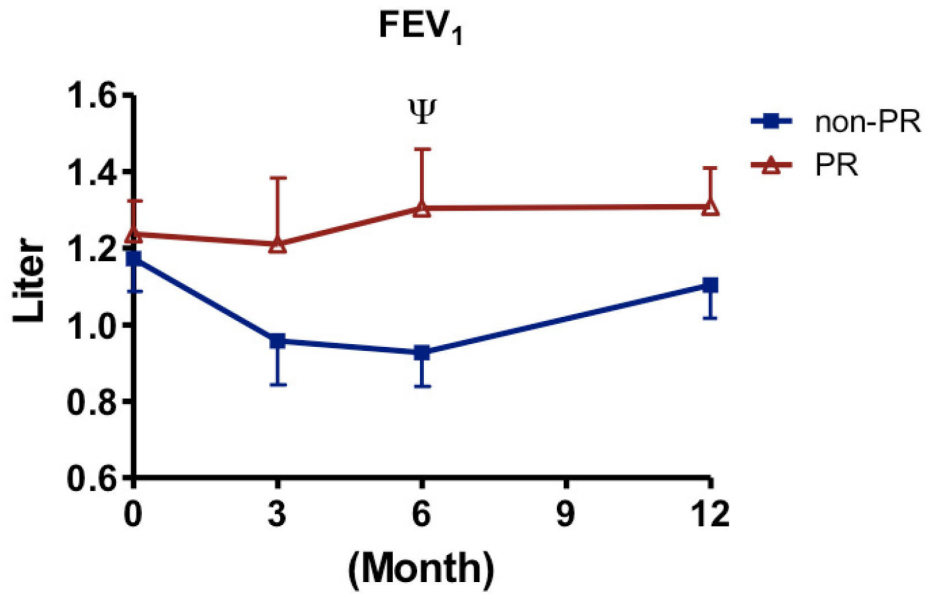


Fig. 2. Forced expiratory volume in 1 second was significantly higher in the PR group at 6 months of the study period. Ψp<0.05, non-PR 6-month FEV_1 vs. PR 6-month FEV_1.

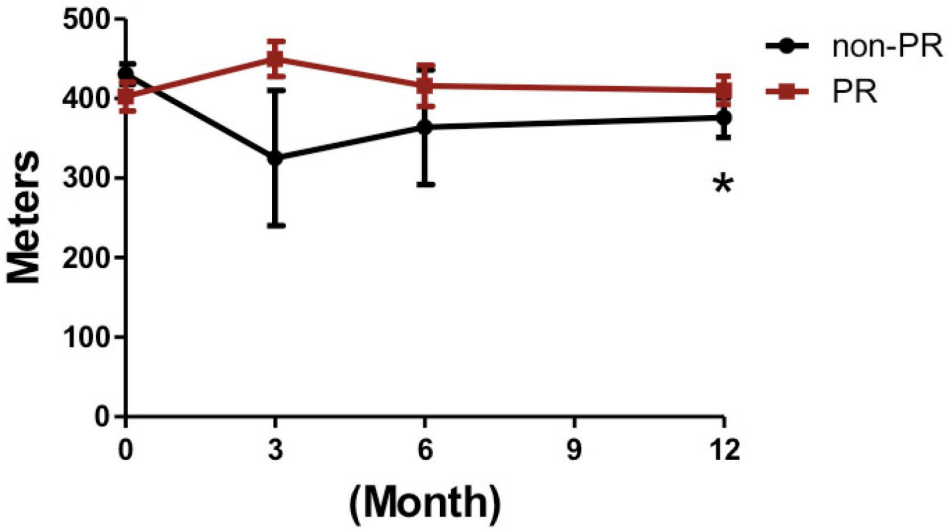


Fig. 3. Six-minute walk distance (6MWD) was maintained in the PR group but significantly declined in the non-PR group. *p<0.05, non-PR group baseline 6MWD vs. 6MWD at 12 months.

Table 2. Clinical Outcomes during the 12-month Study Period

	PR group (n=42)	Non-PR group (n=42)	p
ER visit			
Number of patients (%)	8 (19.0)	17 (40.5)	<0.05
Number of visits (%)	10 (23.8)	39 (92.9)	<0.01
Number of visits (patient^{-1}.yr^{-1})	0.24	0.93	<0.01
Length of ER stay*	15 (0.4)	76 (1.8)	<0.01
Hospitalization			
Number of patients (%)	10 (23.8)	17 (40.5)	<0.05
Number of visits (%)	12 (28.6)	27 (64.3)	<0.05
Number of visits (patient^{-1}.yr^{-1})	0.29	0.64	<0.05
Length of hospital stay*	88 (2.1)	284 (6.8)	<0.05

*Data are expressed as total days (median)

ER stay of 15 days (Table 2). The difference in ER visits was statistically significant.

In terms of hospitalization, 17 of 42 patients (40.5%) in the non-PR group had 27 episodes of hospitalization, with a 6.8-day median length of stay and a 284-day total length of hospitalization (Table 2). In contrast, 10 patients (23.8%) in the PR group (42 patients) had 12 hospitalizations, with a 2.1-day median length of hospital stay and an 88-day total length of hospitalization. These data were significantly lower than those for the non-PR group (p<0.05, respectively) (Table 2).

Discussion

The results of the present study reveal that a 12-month weekly hospital-based PR program can help maintain pulmonary function and enhance exercise capacity in COAD patients, compared to standard care in the OPD. Also, hospital visits and length of stay in the hospital and ER were reduced for COAD patients undergoing rehabilitation programs. The percentage of patients requiring ER visits and hospitalization was significantly decreased, from 40.5% to 19.0% and from 40.5% to 23.8%, respectively, after completing the PR program.

How long should a rehabilitation program be implemented? Three years of PR had a beneficial impact on the rate of FEV_1 decline in a study by Stav *et al*., which showed that a prolonged rehabilitation program inhibited the progression of airflow obstruction in COPD patients. In the PR group, FEV_1 was reduced by 74 ml within 3 years, and in the control group, the reduction was 149 ml [17]. FEV_1 decline may serve as a predictor of risk of death from COPD, and as such, PR should be considered as a disease modifier [18]. One year of outpatient PR was effective intervention leading to significant improvement in exercise tolerance and quality of life in COPD patients, while also reducing disease exacerbation and hospitalization rates [19]. In the current study, 1 year of hospital-based PR could help maintain exercise tolerance but did not change the dyspnea sensation in patients with chronic lung diseases. The ATS/ERS recommends 20 sessions and the ACCP/AACVPR statement suggests that programs of 6-12 weeks are beneficial [12-13]. Zu-Wallack and colleagues [20] suggest that a 10-12 week rehabilitation program (24 sessions) is needed to reach optimal changes in exercise performance, although improvements in quality of life may occur earlier. While their study was limited, relative to the current study, in the lack of focus on individuals, their results were consistent with those of the current study, which shows that the pulmonary function and exercise capacity of COAD patients who do not undergo a PR program are lower after 12 weeks, and will continuously decline and reach a statistical difference at 18 weeks.

The use of PR programs for chronic lung diseases is still controversial. Spontaneous pursed-lip breathing is reportedly a useful technique for increasing walking endurance and reducing oxygen desaturation during walking in patients with moderate-to-severe COPD [21]. Such findings suggest that regular exercise may protect against dyspnea and perceived limitations in walking, both of which are characteristic of progressive chronic lung disease [16]. Therefore, multiple modalities should be included in the PR program to attain maximal effects. This study, in particular, integrated 4 components -- patient education, breathing and lung expansion exercises, bronchial hygiene, and exercise re-conditioning training -- to provide clinically significant benefits in stable COAD patients.

Changes in 6MWD over time are an independent predictor of mortality [22] and an absolute 6MWD threshold of ≥350 meters is associated with the best probability rate of 8-year survival [23]. In addition, patients with the ability to perform a 6MWD ≥350 meters are likely to live better [24]. In this study, more patients were able to reach that threshold after PR (Figure 3). Thus, it can be speculated that the weekly hospital-based program used here may contribute to a better long-term prognosis.

In patients with COPD, hospital admis-

sions and re-admissions account for the majority of healthcare costs [25]. There is mounting evidence that PR also reduces acute healthcare utilization [8]. From a clinical viewpoint, the results here expand the recent findings of Jensen *et al*. [26], in which PR was found to lead to significantly fewer hospitalizations during 6 months of follow-up among stable outpatient COPD patients. The current study also shows the benefits of PR in decreasing the number and length of ER visits, suggesting that long-term hospital-based PR programs may prevent COAD exacerbation and further decrease costs of clinical care.

Nonetheless, further prospective investigations with a large cohort of COAD patients are warranted to confirm the results or expand on the likely benefits of different PR programs for these patients.

Conclusion

Weekly hospital-based PR is feasible and provides a clinically relevant change in pulmonary function and exercise tolerance in stable COAD patients. The number and length of ER visits and hospitalizations during the treatment period are also significantly reduced.

References

1. Celli BR, MacNee W, Agusti A, *et al*. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23: 932-46.
2. Ries AL, Kaplan RM, Limberg TM, *et al*. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 1995; 122: 823-32.
3. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005; 2: 367-70; discussion 371-2.
4. Oudijk EJ, Nijhuis EH, Zwank MD, *et al*. Systemic inflammation in COPD visualised by gene profiling in peripheral blood neutrophils. Thorax 2005; 60: 538-44.
5. Sin DD, Lacy P, York E, *et al*. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 170: 760-5.
6. Carlin BW. Pulmonary rehabilitation and chronic lung disease: opportunities for the respiratory therapist. Respir Care 2009; 54: 1091-9.
7. Cambach W, Wagenaar RC, Koelman TW, *et al*. The long-term effects of pulmonary rehabilitation in patients with asthma and chronic obstructive pulmonary disease: a research synthesis. Arch Phys Med Rehabil 1999; 80: 103-11.
8. Griffiths TL, Burr ML, Campbell IA, *et al*. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000; 355: 362-8.
9. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med 2000; 109: 207-12.
10. Berry MJ, Rejeski WJ, Adair NE, *et al*. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2003; 23: 60-8.
11. Guell R, Casan P, Belda J, *et al*. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest 2000; 117: 976-83.
12. ATS/ERS Pulmonary Rehabilitation Writing Committee. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006; 173: 1390-413.
13. Ries AL, Bauldoff GS, Carlin BW, *et al*. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 2007; 131: 4S-42S.
14. Ho SC, Chiang LL, Cheng HF, *et al*. A pulmonary rehabilitation programme improves lung functional capacity and reduces hospital care cost in patients with chronic obstructive airway disease (COAD) and mucus hypersecretion. Thorac Med 2000; 15: 13-21.
15. Ho SC, Chiang LL, Cheng HF, *et al*. The effect of incentive spirometry on chest expansion and breathing work

in patients with chronic obstructive airway diseases: comparison of two methods. Chang-Gung Med J 2000; 23: 73-9.

16. Heppner PS, Morgan C, Kaplan RM, *et al*. Regular walking and long-term maintenance of outcomes after pulmonary rehabilitation. J Cardiopulm Rehabil 2006; 26: 44-53.
17. Stav D, Raz M, Shpirer I. Three years of pulmonary rehabilitation: inhibit the decline in airflow obstruction, improves exercise endurance time, and body-mass index, in chronic obstructive pulmonary disease. BMC Pulm Med 2009; 9: 26.
18. Sircar K, Hnizdo E, Petsonk E, *et al*. Decline in lung function and mortality: implications for medical monitoring. Occup Environ Med 2007; 64: 461-6.
19. Zwick RH, Burghuber OC, Dovjak N, *et al*. The effect of one year outpatient pulmonary rehabilitation on patients with COPD. Wien Klin Wochenschr 2009; 121: 189-95. [In German English abstract]
20. ZuWallack R, Hashim A, McCusker C, *et al*. The trajectory of change over multiple outcome areas during comprehensive outpatient pulmonary rehabilitation. Chron Respir Dis 2006; 3: 11-8.
21. Faager G, Stahle A, Larsen FF. Influence of spontaneous pursed lips breathing on walking endurance and oxygen saturation in patients with moderate to severe chronic obstructive pulmonary disease. Clin Rehabil 2008; 22: 675-83.
22. Pinto-Plata VM, Cote C, Cabral H, *et al*. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 2004; 23: 28-33.
23. Cote CG, Pinto-Plata V, Kasprzyk K, *et al*. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. Chest 2007; 132: 1778-85.
24. Oga T, Nishimura K, Tsukino M, *et al*. Exercise capacity deterioration in patients with COPD: longitudinal evaluation over 5 years. Chest 2005; 128: 62-9.
25. Lacasse Y, Wong E, Guyatt GH, *et al*. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet 1996; 348: 1115-9.
26. Jensen PS. Risk, protective factors, and supportive interventions in chronic airway obstruction. Arch Gen Psychiatry 1983; 40: 1203-7.

對於慢性阻塞性氣道疾病者每周以醫院爲基礎的肺部復健來維持運動容量及減少住院

李忠恕 * 鍾福財 * 何淑娟 *,** 謝孟亨 * 枋岳甫 * 盛德芳 *
陳麗妃 * 饒文琴 * 林鴻銓 *

前言：這個在台灣三級照護醫院的回溯性研究，目標在評估一個每周以醫院為基礎的監督型肺部復健計畫，對於慢性阻塞性氣道患者的運動容量和臨床表現。

方法：84 位慢性阻塞性氣道患者分成復健組 (PR) 42 人和非復健組 (non-PR) 42 人。復健組中患者接受復健計畫達 12 個月。每三個月肺功能和六分鐘走路測驗會進行一次檢測。另外，將分析全部的住院時間和急診會診。

結果：在肺部復健計畫期間，在復健組六分鐘走路測驗中的距離是維持著 (從 402.5±18.3 到 410.4±17.8 公尺)，但非復健組則明顯下降 (從 430.7±12.8 至 376.0±24.9 公尺，p<0.05)。就用力肺活量 (Forced vital capacity, FVC) 而言，在六個月和十二個時復健組較非復健組大。PR 的每人每年住院次數和住院天數明顯地比 non-PR 減少 (分別為 0.29±0.55 vs. 0.64±1.02 次和 1.88±4.16 vs. 6.71±14.82 天，p<0.05)。相較於 non-PR，觀察的 PR 病人有較低的每人每年急診就醫次數和較少的急診天數 (分別為 0.24±0.53 vs. 0.93±1.67 次和 0.36±0.88 vs. 2.12±4.17 天，p<0.05)。

結論：在慢性阻塞性氣道患者中，以每周醫院為基礎的肺部復健能維持功能性運動容量和改善肺功能。同時，醫院和急診的就醫次數和住院天數也減少。***(胸腔醫學 2017; 32: 115-124)***

關鍵詞：醫院為基礎的肺部復健，慢性阻塞性氣道疾病，運動容量，住院，肺功能

* 長庚醫療體系　台北胸腔內科系　長庚大學醫學院，** 台北醫學大學醫學院　呼吸治療學系
索取抽印本請聯絡：林鴻銓醫師，長庚醫療體系　台北胸腔內科系　長庚大學醫學院，台北市敦化北路 199 號

Tuberculous Abscess of the Anterior Chest Wall: Report of 2 Cases

Li-Liang Chuang*, Jen-Jyh Lee*,**, Chih-Bin Lin*,**

Tuberculosis (TB) usually involves the lungs, which is the site of about 90% of mycobacterial infection. TB of the chest wall is a rare entity. Herein, we reported 2 cases of TB of the chest wall presenting as an abscess without intrapulmonary involvement. Computerized tomography of the thorax showed anterior chest wall abscess without evidence of underlying lung or pleural disease. Sputum examination revealed negative acid-fast bacilli in the smear and TB culture. Both patients were diagnosed by surgical pathology and tissue culture, and were treated with complete resection combined with anti-tuberculous therapy. ***(Thorac Med 2017; 32: 125-129)***

Key words: chest wall abscess, tuberculosis

Introduction

Mycobacterium tuberculosis (Mtb) infection usually involves the lungs. Musculoskeletal tuberculosis (TB) accounts for about 1-3% of patients with TB [1-2], and chest wall involvement is seen in 1% to 5% of all cases with musculoskeletal TB [3]. Due to the lack of specific symptoms and extremely rare manifestations of TB, the diagnosis of chest wall TB is often delayed and remains a challenge.

In the clinical picture, TB of the chest wall may resemble a pyogenic abscess or tumor, and is recognized as an inflammatory soft tissue mass with erosions of the rib or cartilage. TB of the chest wall usually results from hematogenous spread or direct invasion from underlying pleural or pulmonary parenchymal disease [4]. We herein report 2 cases of chest wall TB presenting initially as a mass-like lesion, and that were finally diagnosed through surgical debridement.

Case Reports

Case 1

A 61-year-old female suffered from a right chest wall mass for 1 month. She had dry cough for 1 month and felt localized right chest pain when coughing. She denied fever, weight loss or hemoptysis. Her medical history included type 2 diabetes mellitus (DM) with HbA1c at

*Chest Section, Department of Internal Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan; **Deparment of Medicine, Tzu Chi University, Hualien, Taiwan
Address reprint requests to: Dr. Chih-Bin Lin, Chest Section, Department of Internal Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan, No. 707, Sec. 3, Zhongyang Rd., Hualien City, Hualien County 97071, Taiwan (R.O.C.)

8.1%, treated with oral anti-diabetic drugs only, and hypertension in a stable condition under medication. Her sister had died of breast cancer. She had no history of TB, but lived in an endemic area. Chest computerized tomography (CT) showed a right anterior chest mass with local inflammation, encasing the 3rd to 4th ribs and cartilage, with no evidence of lung or pleural disease (Figure 1). Wide excision of the mass was done and the histopathological examination showed results compatible with TB, presenting with granulomatous inflammation, epithelioid cells and caseous necrosis (Figure 2). Culture of the surgical specimen grew Mtb. Three sets of sputum were negative for acid-fast bacilli stain (AFS) and Mtb culture. A daily regimen of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) was initiated. The patient received anti-tuberculous therapy for 9 months under directly observed therapy (DOT), and she responded well during the follow-up period.

Case 2

A 67-year-old man suffered from a right chest wall mass for 3 months. He had a history of cecal adenocarcinoma and had undergone a right hemicolectomy with regional lymphadenectomy and chemotherapy. Three months after the last chemotherapy session, a right chest wall mass was palpated. The mass enlarged rapidly without tenderness initially, but it became firm, round in shape with a regular border, and painful. CT of the thorax showed cystic lesions around the costo-cartilage junction (Figure 3), without evidence of lung or pleural involvement. Aspiration was performed and turbid yellowish pus was found. He underwent surgical excision, and the histopathological report showed granulomatous inflammation, caseous necrosis and epithelioid cells. The pus culture grew Mtb. The sputum was negative for AFS and TB culture. The patient received anti-tuberculous therapy for 9 months under DOT, with a good clinical response.

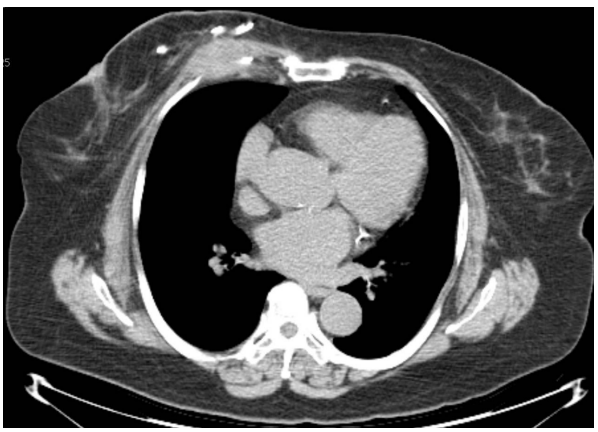


Fig. 1. CT of the thorax showing right anterior chest wall mass with local inflammation, and encased 3rd to 4th ribs and cartilage.

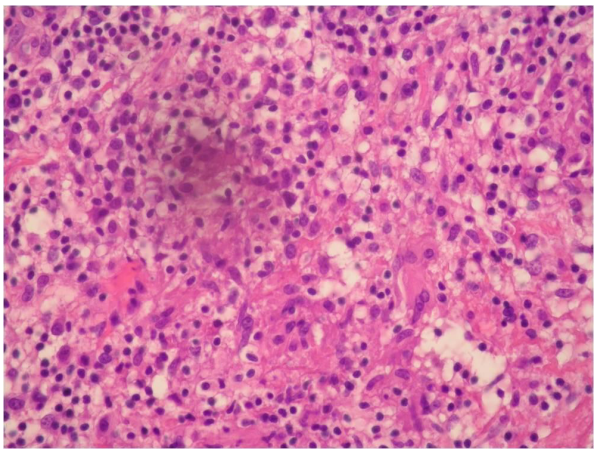


Fig. 2. Histopathological exam showing granulomatous inflammation with epithelioid cells and caseous necrosis.

Discussion

Primary TB of the chest wall is uncommon; its clinical features may resemble pyogenic abscess or tumor, and distinguishing between them can be difficult [5]. Maintaining a high

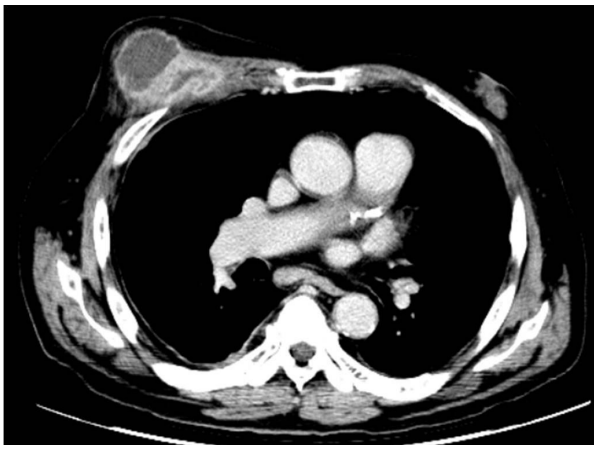


Fig. 3. CT of the thorax showing an abscess formation located at the right anterior chest wall.

degree of suspicion is essential, especially in at-risk groups living in endemic areas. In the first case, the anterior chest wall TB mimicked a breast tumor with local inflammatory signs. Needle aspiration and pus culture did not confirm a pathogen. Pathology after surgical intervention showed granulomatous inflammation, and tissue culture finally confirmed Mtb infection. In the second case, the chest wall TB resembled cancer recurrence. The final diagnosis was dependent upon surgical intervention and pathological confirmation. Both patients were in a relatively immunocompromised status, the former with DM and the latter with colon cancer post-chemotherapy, and they both lived in an endemic area.

The manifestations of chest wall TB on chest roentgenography and CT are non-specific. Bone and costo-cartilage destruction, soft tissue mass with calcification, chest wall mass with low attenuation of central necrosis, and rim enhancement under intravenous contrast medium injection are the most common roentgenographic features of chest wall TB [6]. Both of our patients showed costo-cartilage destruction. However, the first patient presented mass-like lesions, and the latter had mainly cystic lesions with local inflammation.

There are 2 main mechanisms in the pathogenesis of chest wall TB: direct extension from pleural or pulmonary parenchymal disease and hematogenous dissemination of a dormant tuberculous focus [7]. We speculate both cases may have resulted from the latter.

Surgical intervention and histological examination are usually necessary for the diagnosis and treatment of chest wall TB. Some case series [8] have reported good results with anti-TB drugs alone. But in other series [9], abscesses were not cured and even recurred or progressed despite adequate medical treatment. The chest wall abscesses in both of our patients were resected, and diagnosed via pathology report and tissue culture.

Tobias *et al* [10] mentioned that the significant predictors of poor long-term outcome in extra-pulmonary TB (EPTB) were age at diagnosis, treatment duration, type of EPTB and HIV-infection. Mortality among patients with EPTB was higher for those with TB meningitis and lower for those with genitourinary TB. The treatment course for patients with chest wall TB without pulmonary involvement was recommended to be about 6 months [10-11]. The treatment course for our 2 patients was extended to 9 months, due to extra-pulmonary involvement and an immunocompromised status in both patients. The treatment response was satisfactory in both patients.

Conclusion

Our report highlights the importance of an awareness of chest wall TB in Taiwan, where the incidence of TB is intermediate. Clinicians

should maintain a high degree of suspicion when the patient is immunocompromised and complains of chest wall pain, with mass or abscess formation. Chest CT is recommended for the diagnosis; however, the final confirmation depends on histopathology and mycobacterial cultures. Complete resection and postoperative anti-tuberculous medication are essential for disease cure and prevention of recurrence. The clinical outcome is generally satisfactory.

References

1. Yao DC, Sartoris DJ. Musculoskeletal tuberculosis. Radiol Clin North Am 1995; 33: 679-89.
2. Goldberg I, Avidor I. Isolated tuberculous tenosynovitis of the Achilles tendon: a case report. Clin Orthop 1985; 194: 185-8.
3. Morris BS, Maheshwari M, Chalwa A. Chest wall tuberculosis: A review of CT appearances. Br J Radiol 2004; 77: 449-57.
4. Ueno T, Yoshioka T, Satoh H, *et al*. Chest wall tuberculosis. Respiration 2001; 68: 87.
5. Paik HC, Chung KY, Kang JH, *et al*. Surgical treatment of tuberculous cold abscess of the chest wall. Yonsei Med J 2002; 43: 309-14.
6. Lee G, Im JG, Kim JS, *et al*: Tuberculosis of the ribs: CT appearance. J Comput Assist Tomogr 1993; 17: 363-6.
7. Faure E, Souilamas R, Riquet M, *et al*. Cold abscess of the chest wall: a surgical entity? Ann Thorac Surg 1998; 66: 1174-8.
8. Burke HE. The pathogenesis of certain forms of extrapulmonary tuberculosis: spontaneous cold abscesses of chest wall and Pott's disease. Am RevTuberc 1950; 62: 48-67.
9. Chen CH, Shih JF, Wang LS, *et al*. Tuberculous subcutaneous abscess: analysis of seven cases. Tuber Lung Dis 1996; 77: 184-7.
10. Pusch T, Pasipanodya JG, Hall RG, *et al*. Therapy duration and long-term outcomes in extra-pulmonary tuberculosis. BMC Infect Dis 2014; 14: 115.
11. Kim YJ, Jeon HJ, Kim CH, *et al*. Chest wall tuberculosis: clinical features and treatment outcomes. Tuberc Respir Dis 2009; 67(4): 318-24.

前胸壁結核菌膿瘍－病例報告

莊立良 * 李仁智 *,** 林智斌 *,**

結核病是受結核桿菌感染而引起的，主要以影響肺部的一種疾病，約佔全部百分之九十，而胸壁的侵犯是較罕見的一類。在本文中，我們報導了兩個前胸壁結核膿瘍的案例，病患的胸部電腦斷層掃描顯示前胸壁膿瘍，並無伴隨其他肺部或肋膜疾病。痰液抹片與培養皆為陰性。病患經過手術切除，由病理組織培養證實為結核菌感染，最後服用抗結核藥物治療完全治癒。*(胸腔醫學 **2017; 32: 125-129**)*

關鍵詞：胸壁膿瘍，結核菌

* 佛教慈濟醫療財團法人花蓮慈濟醫院 內科部 胸腔內科，** 慈濟大學醫學系
索取抽印本請聯絡：林智斌醫師，佛教慈濟醫療財團法人花蓮慈濟醫院 內科部 胸腔內科
97071 花蓮縣花蓮市中央路 3 段 707 號

Tracheal Diverticulum Presentinged as Long-Term Hoarseness: Case Report and Literature Review

Cheng-Che Tu, Wen-Hu Hsu

Tracheal diverticulum is a rare disease entity, usually found in asymptomatic patients, or those presenting with cough, dyspnea, and sometimes, dysphagia. Tracheal diverticula are classified as congenital or acquired based on their anatomic position and characteristics. Congenital diverticula are usually smaller, located 4 or 5 cm below the vocal cord. The acquired form is larger, presents in adulthood, typically protrudes from the right posterolateral wall of the trachea, and has a wider opening, if any. On histologic examination, tracheal diverticula have respiratory mucosa only, without components of cartilage or smooth muscle. The association between chronic obstructive pulmonary disease and tracheal diverticula is still being debated. Cases of recurrent laryngeal nerve paralysis and hoarseness caused by tracheal diverticula, with full recovery after resection, have been reported previously. If medical treatment of patients with symptomatic tracheal diverticulum fails, surgical resection is a feasible option.

We report a rare case of tracheal diverticulum that presented with hoarseness, and review related published articles. Although relatively rare, tracheal diverticulum should be included in the differential diagnosis of hoarseness. ***(Thorac Med 2017; 32: 130-135)***

Key words: tracheal diverticulum, hoarseness, chronic obstructive pulmonary disease

Introduction

Tracheal diverticulum is a rare thoracic disease entity. It is usually asymptomatic, and presents on radiological examination as an incidentally found paratracheal air collection. There are a few reports of symptomatic cases - for some patients, tracheal diverticulum was the cause of chronic cough, and other patients presented with difficult intubation or recurrent laryngeal nerve palsy. Tracheal diverticula are often classified into 2 groups: congenital or acquired. The cause of tracheal diverticulum remains unclear; some reports suggested acquired tracheal diverticulum is associated with increased intraluminal pressure on the trachea, which is expected in patients with obstructive lung disease and emphysema. We present the case of a 68-year-old male who presented with intermittent hoarseness and foreign body sensation in the neck. With the aid of chest computed tomography (CT), he was diagnosed as having tracheal diverticulum, and underwent diverticulectomy. The pathology showed a cystic struc-

Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Cheng-Che Tu, Division of Thoracic Surgery, Department of Surgery, Taipei-Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan

ture lined with respiratory epithelium.

Case Report

A 68-year-old male patient came to our chest surgery outpatient clinic with the complaint of intermittent hoarseness and foreign body sensation for 3 months. He also mentioned that he had sudden cough fits from time to time, which had been noted for more than 1 year. He had a tobacco smoking habit of ½-1 pack per day for 20 years. He had no significant systemic diseases, such as hypertension, diabetes mellitus or chronic obstructive pulmonary disease (COPD). Physical examination revealed normal vital signs, and no obvious swelling or deviated trachea around his neck. Chest auscultation of the bilateral hemithorax was clear. His laboratory results were all unremarkable. Chest film revealed only mildly increased right lower lung infiltration. A chest CT was performed, and revealed a small paratracheal air cyst, 2.5×1.2 cm in size, spanning from the T1 to the T2 level, abutting the right posterior wall of the trachea, with minimal infiltration at the bilateral basal lungs. Tracheal diverticulum was suspected (Figure 1). A 3D reconstruction of the CT scan and a bronchoscopy examination were arranged. The 3D reconstruction image revealed a tracheal diverticulum at the right posterior aspect of the trachea, about 2.0×1.0×1.5 cm in size, with a very thin connecting stalk reaching the posterior wall of the trachea (Figure 2). However, the bronchoscopy examination failed to find this endotracheal connection or an opening to the diverticulum.

The patient's lung function test showed a forced expiration volume in 1 second (FEV_1) of 2.14 liters, 88% of predicted value; the ratio of FEV_1 to functional vital capacity (FVC) was 82%. There was no increased airway resistance, and the diffusion capacity for carbon monoxide (DLCO) was 69%. With his available medical history and physical examination, as well as the imaging studies mentioned above, we found no possible cause for his intermittent hoarseness other than the tracheal diverticulum. Surgical removal of the diverticulum was a feasible option for the patient. We discussed this with him and he agreed to the surgery.

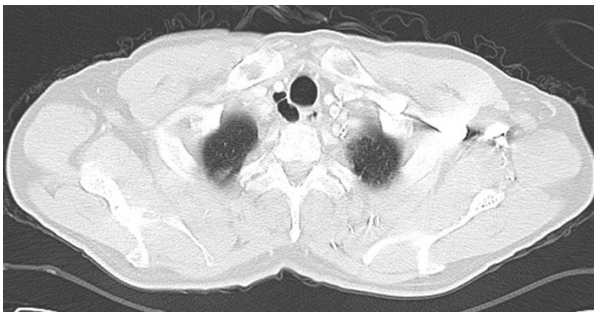


Fig. 1. CT image of tracheal diverticulum

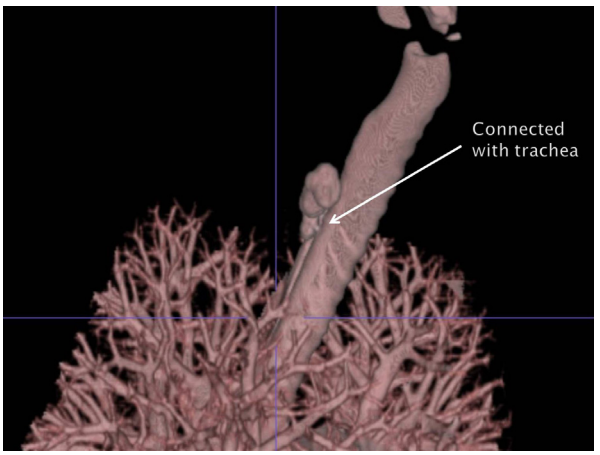


Fig. 2. 3D reconstruction of CT image, showing the tracheal diverticulum was attached to the tracheal wall with a thin stalk.

The surgery was performed using an open method. A 7-cm oblique incision was made at his right neck, in line with the anterior border of the sternocleidomastoid muscle. The wound was deepened, the sternocleidomastoid muscle

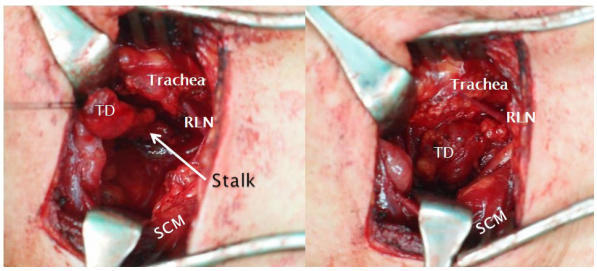


Fig. 3. Operative findings during the surgery, showing the tracheal diverticulum connected to the trachea. TD: tracheal diverticulum, RLN: recurrent laryngeal nerve, SCM: sternocleidomastoid muscle

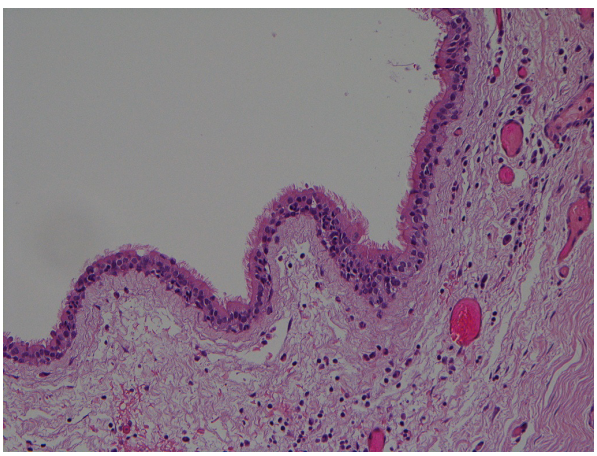


Fig. 4. Histopathological findings of tracheal diverticulum.

was retracted backward, the omohyoid muscle was divided, and the trachea was revealed. A cystic lesion at the right posterior wall of the trachea was revealed, attached to the trachea with a pedicle (Figure 3). Complete resection of the tracheal diverticulum and suture ligation of the pedicle were performed. Histopathological examination showed a cystic lesion lined with respiratory-type mucosal tissue with a fibrotic wall. Some fibro-adipose tissue was also noted. No cartilage was identified. This picture was consistent with that of an acquired tracheal diverticulum (Figure 4). All in all, the findings confirmed the diagnosis of tracheal diverticulum. The patient was discharged and had an uneventful recovery. Mild hoarseness was noted in the first 2 months of a 6-month follow-up, but the symptom gradually lessened with time.

Discussion

There are several forms of paratracheal air cyst, such as tracheal diverticulum, lymphoepithelial cyst, and bronchogenic cyst. Most of them now are thought to be tracheal diverticulum. [1] Tracheal diverticulum is a rare clinical entity. A previous study reported a 1% incidence of tracheal diverticulum encountered in autopsies, and in a more recent study, tracheal diverticulum could be found on CT examinations of 2%~3.7% of patients [2-3]. Tracheal diverticulum is an evagination of the tracheal wall, consisting only of respiratory epithelial lining, with no smooth muscle or cartilage. There are 2 types of tracheal diverticula: congenital and acquired. The acquired form is thought to be a result of mucosal herniation, and is usually located at the T2 level of the right posterior aspect of the trachea. Congenital tracheal diverticula are thought to be malformed supernumerary branches of the trachea [4].

In our study, the neck connecting the trachea with the air cyst was not observed with bronchoscopy. However, this connection is not found in most cases. According to Goo *et al* [5], only 8% of tracheal diverticula were linked with the trachea. Buterbaugh *et al* [3] found that 9 in 26 patients with paratracheal air cyst had this communication. Kurt *et al* [6] examined 12,512 patients with chest CT, and discovered 412 tracheal diverticula in 299 patients. They found communication with the trachea in 12.9% of the diverticula. Sometimes, the communication is not evident on multidetector CT,

but is visible with coronal or sagittal images. This may be because the communication between the trachea and the diverticulum is a fibrous connection or has a very thin neck. In our report, the connection was not seen very clearly in the axial planes, but was discovered with the coronal cuts and in the 3D reconstructed image. Although the bronchoscopy examination did not reveal the communication in our patient, in some cases, it might be a narrow-necked or fibrous connection. Goo *et al* proposed that, since the paratracheal air cyst and tracheal diverticulum have the same histological composition, and an air cyst is frequently a diverticulum with a degenerated or diminished connecting stalk, it is very possible that these similar lesions with paratracheal air accumulation are all tracheal diverticulum in the first place [5]. However, more clinical series reports and pathological analyses are needed to support this suggestion.

The relationship between tracheal diverticulum and COPD is controversial. Goo *et al* [5] suggested that paratracheal air cysts might be a sign of COPD. They found significantly lower FEV_1/FVC and FEF 25-75% in patients with paratracheal air cyst than in those in the control group. However, Buterbaugh *et al* [3] found no significant association between paratracheal cystic lesions and COPD. Kurt *et al* [6] also found no association between these 2 conditions. Many patients in their study were discovered incidentally and at a young age; thus, the anticipated rate of having COPD would be low. Many of the tracheal diverticula found in the Kurt *et al* study might have been undiscovered congenital diverticula; however, they did find an association between hyperinflation and bronchial diverticulum. Two earlier studies also support this finding. In 1 of the 2 studies, Sverzellati *et al* found a connection between multiple bronchial diverticula and impaired pulmonary function [7-8]. In our study, the patient had long-term sudden coughing and intermittent hoarseness symptoms, but the symptoms did not last long each time. The cough was generally a dry cough, and there were no other symptoms associated with COPD. His pulmonary function was within a normal range.

Although many tracheal diverticula are asymptomatic, a patient with tracheal diverticulum may present with recurrent respiratory tract infections, cough, dyspnea, hemoptysis, painful neck swelling, cervical abscess, globus pharygeus, respiratory distress, and sometimes, dysphagia [9]. Patients presenting with hoarseness are very rare. Chaudhry *et al* reported a 54-year-old nonsmoking woman who presented with mild cough and hoarseness for 2 months; chest CT revealed a tracheal diverticulum [10].

If a tracheal diverticulum is found incidentally, the patient should be followed up. Tracheal diverticulum can serve as a reservoir and cause recurrent infection, so antibiotics and mucolytic agents can be used. In patients with symptoms, the diverticulum can be treated surgically or with laser cauterization. Collin *et al* has described a surgical procedure for tracheal diverticulum [11].

In conclusion, tracheal diverticulum is a rare disease, and is generally classified into congenital and acquired types. The association of this entity with COPD is equivocal. Tracheal diverticulum presenting with hoarseness is extremely rare, but tracheal diverticulum could still be 1 of the differential diagnoses of hoarseness. Treatment options include conservative, endoscopic and surgical modalities.

References

1. Cheng HM, Chang PY, Chiang KH, *et al*. Prevalence and characteristics of paratracheal air cysts and their association with emphysema in a general population. Eur J Radiol 2012; 81: 2673-7.
2. MacKinnon D. Tracheal diverticula. J Pathol Bacteriol 1953; 65: 513-7
3. Buterbaugh JE, Erly WK. Paratracheal air cyst: A common finding on routine CT examinations of the cervical spine and neck that may mimic pneumomediastinum in patients with traumatic injuries. AJNR Am J Neuroradiol 2008; 29: 1218-21.
4. Frenkiel S. Assimes 1K, Rosales JK. Congenital tracheal diverticulum: a case report. Ann Otol Rhinol Laryngol 1980; 89: 406-8.
5. Goo JM, Im JG, Ahn JM, *et al*. Right paratracheal air cyst in the thoracic inlet: Clinical and radiologic significance. AJR Am J Roentgenol 1999; 173: 65-70.
6. Kurt A, Sayit AT, Ipek A, *et al*. A multidetector computed tomography survey of tracheal diverticulum. Eurasian J Med. 2013 Oct; 45(3): 145-8.
7. Sanford MF, Broderick. Multidetector computed tomography detection of bronchial diverticula. J Thorac Imaging 2007; 22: 265-7.
8. Sverzellati N, Ingegnoli A, Calabro E, *et al*. Bronchial diverticula in smokers on thin-section CT. Eur J Radiol 2010; 20: 88-94.
9. Soto-Hurtado EJ, Peñuela-Ruíz L, Rivera-Sánchez I, *et al*. Tracheal diverticulum: a review of the literature. Lung. 2006 Nov-Dec; 184(6): 303-7. Epub 2006 Nov 3.
10. Chaudhry I, Mutairi H, Hassan E, *et al*. Tracheal diverticulum: a rare cause of hoarseness of the voice. Ann Thorac Surg. 2014 Feb; 97(2): e29-31.
11. Collin JD, Batchelor T, Hughes CW, *et al*. Transcervical repair of tracheal diverticulum. Ann Thorac Surg. 2014 Oct; 98(4): 1490-2.

以聲音嘶啞表現的氣管憩室

杜承哲　許文虎

氣管憩室是一少見的疾病，病患可能無症狀，或以咳嗽、呼吸急促或有時以吞嚥困難表現。氣管憩室可依據其解剖學常見位置及其他特徵，區分為先天型及後天型。先天型之氣管憩室通常較小，常位在聲帶下方四到五公分處。後天型的可能較大，在成年時表現，通常從氣管的右後側方突出，如有開口，則具有較寬的開口。在病理學檢查下，氣管憩室全部由呼吸道上皮所組成，並不含有軟骨或肌肉之成分。氣管憩室與慢性阻塞性肺病的關聯，現在仍有爭議。氣管憩室造成喉返神經之壓迫，並且造成聲音嘶啞，在接受手術後復原的案例曾被報導過。若內科治療不成功，外科治療為一可行之選項。

我們報告一位以聲音嘶啞表現的氣管憩室病患，以及文獻的回顧。雖然這樣的表現相當稀少，但氣管憩室仍可以是聲音嘶啞的鑑別診斷之一。*(胸腔醫學* ***2017; 32: 130-135)***

關鍵詞：氣管憩室，聲音嘶啞，慢性阻塞性肺病

台北榮民總醫院　外科部　胸腔外科
索取抽印本請聯絡：杜承哲醫師，台北榮民總醫院　外科部　胸腔外科，台北市石牌路二段 201 號

Fatal Salmonella-Infected Aneurysm of the Aortic Arch: A Case Report

Fu-Hsiung Yang, Chih-Feng Chian, Wann-Cherng Perng, Shih-Wei Wu

An infected arterial aneurysm is often caused by *Staphylococcus aureus* or Salmonella species, and involvement of the aorta is a rare but life-threatening condition. The mortality rate is very high in those without surgical treatment. The typical presentation of an infected aneurysm is based on its location, whether it is in a superficial location (e.g., common femoral artery, a painful, pulsatile mass with fever) or is a deeper vessel (e.g., aorta, fever with or without blood-tinged sputum). Because of the insidious onset, symptoms and signs could occur after rupture of the aneurysm. Here, we describe a fatal case of infected aneurysm of the aortic arch mimicking pneumonia and caused by Salmonella group D. ***(Thorac Med 2017; 32: 136-141)***

Key words: infected aneurysm of the aortic arch, Salmonella

Introduction

Clinical manifestations of infected aneurysms are diversely characterized by systemic symptoms of occult infection and symptoms localized to the involved artery or life-threatening rupture with hemorrhage [1]. Thoracic aorta involvement usually presents with nonspecific chest pain or blood-tinged sputum, but may be asymptomatic until the aneurysm ruptures and hemorrhage occurs. Salmonella species are often the microorganism responsible for infected aortic aneurysm, especially in Taiwan [2]. Early detection of infected aortic aneurysm and prompt surgical intervention are crucial to the outcome. Image study with computed tomography (CT) or magnetic resonance imaging is most useful for diagnosing an infected aneurysm. Here, we describe a fatal case of infected aneurysm of the aortic arch caused by Salmonella group D.

Case Report

A 59-year-old divorced Taiwanese man had a chest X-ray (CXR) and chest CT scan 1 month before admission because he feared he might have lung cancer. Both CXR and CT revealed no remarkable findings (Figure 1A, 1B). General malaise developed 1 week before admission and he began to have productive cough with blood-tinged sputum 3 days before

Division of Pulmonary and Critical Care, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
Address reprint requests to: Dr. Shih-Wei Wu, Division of Pulmonary and Critical Care, Department of Internal Medicine, Tri-Service General Hospital, No. 325, Cheng-Kung Road, Sec. 2, Taipei 114, Taiwan, Republic of China

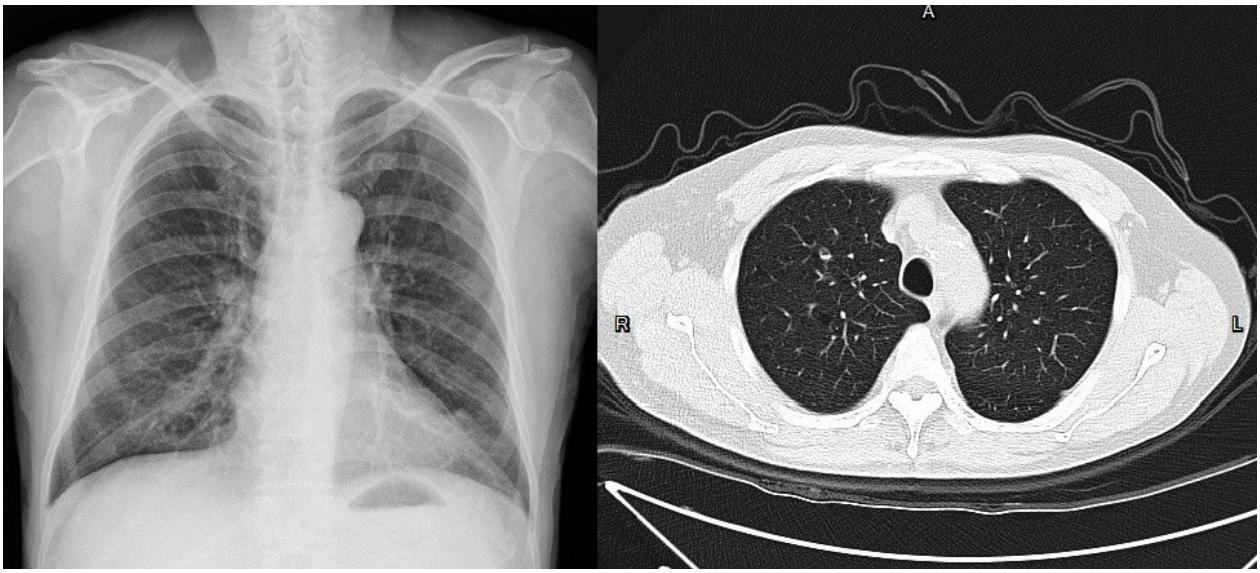


Fig. 1. Chest X-ray and CT scan taken 1 month prior to admission show no obvious abnormality.

admission. Then, he called at our emergency department due to fever up to 40°C on the day of admission. The patient had a medical history of type 2 diabetes mellitus, hypertension, hyperlipidemia, alcoholism and depressive disorder with medication at our hospital for 10 years. There were no significant findings in his family history. The patient had a habit of smoking (1~2 packs of cigarettes per day for 30 years) and drinking (liquor with 40% alcohol, 300ml per day for 30 years).

At the emergency department, his blood pressure was 172/96 mmHg, pulse rate 122 beats/min, body temperature 40.2°C and respiratory rate 22 breaths/min. An oxygen nasal cannula with 3 L/min was required to maintain a pulse oximeter oxygen saturation above 90%. On auscultation, there were regular rapid heartbeats without gallop, rubs, murmurs, crackles or rhonchi. His CXR revealed a patchy consolidation shadow in the left upper lobe (LUL), adjacent to the aortic arch (Figure 2). Laboratory tests disclosed a white blood cell count of 13100/μL with 82% neutrophils, hemoglobin 12.4 g/dL, platelets 395,000/μL, C-reactive protein (CRP) 27.29 mg/dL and glucose 275 mg/

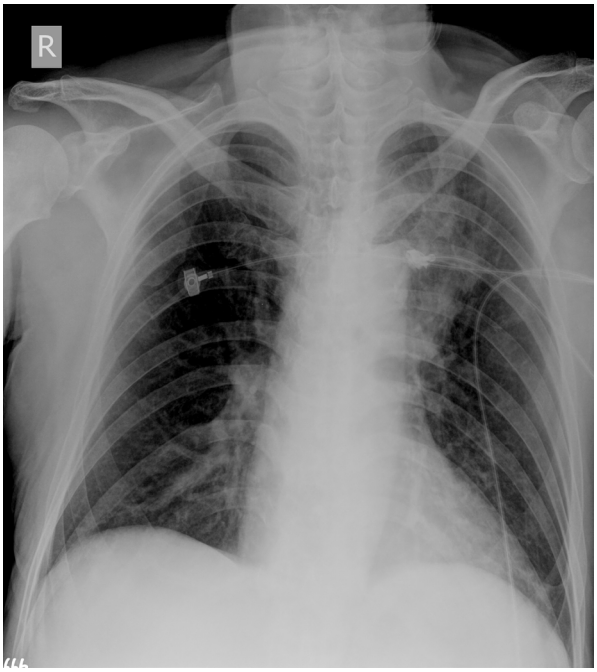


Fig. 2. Chest X-ray at admission shows a patchy consolidation shadow in the left upper lobe adjacent to the aortic knob.

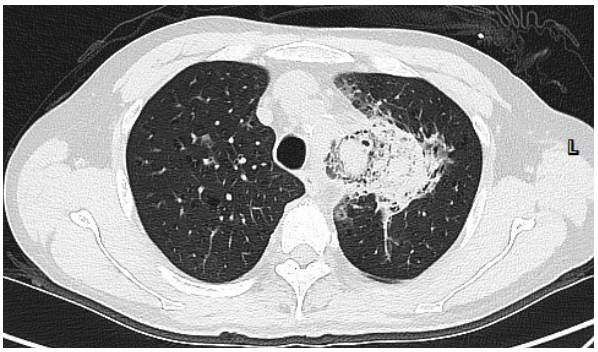


Fig. 3. Chest CT without contrast medium on the day of admission shows patchy consolidation with air in the LUL adjacent to and invading the mediastinum, a nodular lesion (size: about 2.7 cm) inside the aortic arch and atherosclerotic change in the aorta.

dL. Arterial blood gas examination revealed pH: 7.459, $PaCO_2$ 34.9 mmHg, HCO_3^- 25 mmol/L, PaO_2 61.8 mmHg and SaO_2 91.6%. A rapid screen for influenza A/B was negative. He then was admitted for further management.

After admission, we arranged a chest CT scan which revealed an aortic arch with an irregular arterial wall, with peri-aortic soft-tissue inflammation and peri- and intra-aortic gas (Figure 3). Infected aneurysm of the aortic arch was diagnosed based on CT scan findings. The infectious disease specialist prescribed ceftazidime 2 gm intravenous 3 times daily on the day of admission and we consulted a cardiac surgeon for possible surgical intervention. Blood and sputum samples for bacterial, fungal and mycobacterial cultures were also collected before we started antibiotics. However, a sudden cardiac arrest occurred on the same day. The patient eventually died despite cardiovascular life support. Later, blood culture reported Salmonella group D susceptible to ceftazidime.

Discussion

The clinical manifestations of infected thoracic aortic aneurysm are often nonspecific, and the diagnosis is often delayed until the aneurysm ruptures or leaks. CT angiography can definitively diagnose the aneurysm, which is characterized by a saccular or eccentric aneurysm, peri-aortic edema, peri-aortic soft tissue inflammation or mass and peri-aortic gas [3]. Our patient presented to the emergency department with fever, productive cough with blood-tinged sputum, a patchy consolidation shadow in the LUL of the lung adjacent to the aortic knob, leukocytosis and elevation of CRP. These manifestations led to a presumptive diagnosis of pneumonia. However, after admission, infected aneurysm of the aortic arch was promptly considered based on the typical appearance of the chest CT scan. Although the patient died suddenly, probably of aneurysm rupture, the diagnosis of an infected aneurysm of the aortic arch was confirmed after blood culture grew Salmonella group D.

Osler first described a case of mycotic aneurysm from infective endocarditis in 1885 [4]. Sower and Whelan found that Salmonella was a common cause of mycotic aneurysm in patients with preexisting atherosclerosis [5]. The pathogenesis of mycotic aneurysm has been attributed to 4 different mechanisms [6], including: (1) septic embolization occluding the vasa vasorum or vessel lumen, causing vessel wall infection and aneurysm formation; (2) an adjoining inflammatory process outside the vessel wall extending to a nearby artery; (3) inoculation of bacteria at the time of vascular injury (e.g., intravenous drug abuse or iatrogenic puncture), and (4) bacteremic seeding of an existing intimal injury (e.g., atherosclerosis of the aorta).

The atherosclerotic aorta seems to be vulnerable to Salmonella, and the pathophysiology is bacteremic seeding of an existing intimal injury [7].

In Western countries, the microorganisms most commonly responsible for infected aortic aneurysm are *Staphylococcus aureus* and Streptococcus species, followed by Salmonella species, but in Taiwan, the most common causative microorganism is Salmonella species [1,2,7]. *Escherichia coli* and *Mycobacterium tuberculosis* have also been reported in both Taiwan and the USA [7-8]. Non-typhoid Salmonella are important food-borne pathogens that cause gastroenteritis, bacteremia without gastroenteritis and focal metastatic infection subsequent to bacteremia [9]. Traditional risk factors for atherosclerosis include old age, diabetes and hypertension [10]. Patients with atherosclerosis of the aorta are predisposed to endovascular infection secondary to bacteremia. The pathogenesis of endovascular infection due to Salmonella consists of 3 steps: consumption of contaminated food, survival and proliferation of bacteria in macrophages and establishment of endovascular infection [11-12]. A study in Taiwan by Hsu RB [13] found that patients with diabetes mellitus, hypertension, coronary artery disease, peripheral arterial occlusive disease, ischemic stroke, human immunodeficiency virus infection, cancer, and those under chemotherapy, were susceptible to non-typhoid Salmonella bacteremia and endovascular infection. Our patient had diabetes and hypertension, which led to the development of atherosclerosis of the aorta and predisposed him to Salmonella bacteremia with subsequent endovascular infection.

The standard treatments for infected aneurysm are antibiotic therapy combined with surgical debridement, graft or patch repair, with or without revascularization. Hsu *et al* reported that patients who received only antibiotic treatment had high in-hospital mortality (55%), while those with surgical intervention had a much better outcome (mortality 11%) [2]. Antibiotic treatment for Salmonella bacteremia generally involves a bactericidal drug, such as a third-generation cephalosporin or a fluoroquinolone [9]. However, due to the recent trend of resistant Salmonella, life-threatening infection such as infected aneurysm of the aorta should be treated with both a third-generation cephalosporin and a fluoroquinolone until susceptibilities of Salmonella are known [9]. The duration of antibiotic therapy is at least 6 weeks if surgical treatment is successful. Surgical intervention can be performed through open debridement and aneurysm repair or endovascular stent grafting. Endovascular stent grafting may be performed for patients for whom open surgical debridement and aneurysm repair would be too risky. It can also be a temporary treatment for patients with aneurysm rupture [14]. However, in the treatment of infected aortic aneurysm, endovascular stent grafting may fail because of the lack of debridement. Overall, debridement and in situ reconstruction of the aortic aneurysm remain the preferred procedure. In this case, we administered adequate antibiotics with ceftazidime 2 gm intravenously 3 times daily and requested assessment of surgical intervention without delay. Although the isolated Salmonella species was sensitive to ceftazidime, the disease progressed catastrophically probably due to the lack of timely surgical intervention [2,15].

In conclusion, infected aneurysm of the thoracic aorta is an uncommon but life-threatening condition. Early diagnosis and aggressive surgical and antibiotic treatment are crucial to a successful outcome. Early diagnosis requires

clinical alertness and awareness of the imaging appearances, especially early changes. We should keep in mind that with the appearance of any patchy shadow adjacent to the aortic region, the possibility of an aortic lesion should be included in the differential diagnosis, especially in relatively immunocompromised patients. Further diagnostic procedures and management should be performed promptly to avoid a fatal outcome.

References

1. Muller BT, Wegener OR, Grabitz K, *et al*. Mycotic aneurysms of the thoracic and abdominal aorta and iliac arteries: experience with anatomic and extra-anatomic repair in 33 cases. J Vasc Surg 2001; 33(1): 106-13.
2. Hsu RB, Chen RJ, Wang SS, *et al*. Infected aortic aneurysms: clinical outcome and risk factor analysis. J Vasc Surg 2004; 40(1): 30-5.
3. Lee WK, Mossop PJ, Little AF, *et al*. Infected (mycotic) aneurysms: spectrum of imaging appearances and management. Radiographics 2008; 28: 1853-68.
4. Osler W. The Gulstonian lectures on malignant endocarditis. Br Med J 1885; 1: 467-70.
5. Sower ND, Whelan TJ Jr. Suppurative arteritis due to Salmonella. Surgery 1962; 52: 851-9.
6. Johansen K, Devin J. Mycotic aortic aneurysms. A reappraisal. Arch Surg 1983; 118: 583-8.
7. Hsu RB, Tsay YG, Wang SS, *et al*. Surgical treatment for primary infected aneurysm of the descending thoracic aorta, abdominal aorta, and iliac arteries. J Vasc Surg 2002; 36: 746-50.
8. Miller DV, Oderich GS, Aubry MC, *et al*. Surgical pathology of infected aneurysms of the descending thoracic and abdominal aorta: clinicopathologic correlations in 29 cases (1976 to 1999). Hum Pathol 2004; 35(9): 1112-20.
9. Hohmann EL. Nontyphoidal salmonellosis. Clin Infect Dis 2001; 32: 263-9.
10. Fruchart JC, Nierman MC, Stroes ES, *et al*. New risk factors for atherosclerosis and patient risk assessment. Circulation 2004; 109: III15-9.
11. Darwin KH, Miller VL. Molecular basis of the interaction of Salmonella with the intestinal mucosa. Clin Microbiol Rev 1999; 12: 405-28.
12. Ohl ME, Miller SI. Salmonella: a model for bacterial pathogenesis. Annu Rev Med 2001; 52: 259-74.
13. Hsu RB, Lin FY. Risk factors for bacteraemia and endovascular infection due to non-typhoid salmonella: a reappraisal. QJM 2005; 98: 821-7.
14. Inoue H, Iguro Y, Yamamoto H, *et al*. Palliative stent-graft insertion followed by an allograft replacement for an infected and ruptured aortic aneurysm. Ann Thorac Cardiovasc Surg 2009; 15: 261-4.
15. Crump JA, Sjolund-Karlsson M, Gordon MA, *et al*. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella infections. Clin Microbiol Rev. 2015; 28: 901-37.

非傷寒性沙門氏桿菌感染之致命性主動脈弓血管瘤：病例報告

楊福雄　簡志峰　彭萬誠　吳世偉

感染性動脈瘤 (infected aneurysm) 常是由金黃色葡萄球菌 (*Staphylococcus aureus*) 或非傷寒沙門氏桿菌屬 (Salmonella species) 所引起的感染性血管瘤。其中的主動脈血管瘤是罕見且常致命的併發症，症狀以非特異性的胸痛、血痰、發燒來表現，甚至有些直到血管瘤破裂才發現，故死亡率很高，尤其是未作外科治療者死亡率更高。因此，即時的診斷與處置相當重要。我們的案例報告是一位 59 歲男性，有糖尿病及高血壓病史，因發燒和咳嗽帶有血絲痰至本院急診室求治，經影像學評估可能是感染性主動脈瘤，住院後給予廣效型抗生素治療及會診心血管外科醫師做手術治療的評估；但是不久之後突然心臟停止，經過急救後，病人仍然死亡。死亡後其生前所作之血液培養長出沙門氏桿菌 (Salmonella group D)。*(胸腔醫學 2017; 32: 136-141)*

關鍵詞：感染性主動脈弓血管瘤，非傷寒性沙門氏桿菌

三軍總醫院　內科部　胸腔內科
索取抽印本請聯絡：吳世偉醫師，三軍總醫院　內科部　胸腔內科，台北市內湖區成功路二段 325 號

Three Metachronous Primary Malignancies: A Case Report and Literature Review

Ying-Tang Fang*, Kuo-Tung Huang*, Chin-Chou Wang*,**,***

A 63-year-old male who had been diagnosed as having esophageal squamous cell carcinoma (T1N0Mx post- endoscopic submucosal dissection) in 2011 presented with a left soft palate mass in 2012. Biopsy of the oral mucosa was performed and the pathology showed well-differentiated squamous cell carcinoma. This patient presented to Chang Gung Memorial Hospital in 2014 with blood-tinged sputum and progressive dyspnea. Initial chest x-ray showed right upper lobe consolidation. Chest CT examination revealed right upper lobe consolidation with a suspicious 6cm infiltrative mass invading the right hilum and mediastinum. Multiple liver nodules and masses in both lobes of the liver were also noted. Bronchoscopy examination with tissue biopsy for pathologic study revealed small cell carcinoma of the bronchus. Echo-guided fine needle aspiration for the right liver lobe tumor was performed and the pathology study showed small cell carcinoma, metastatic. The initial approach to patients with suspected lung cancer is based on the study results of patients with non-small cell lung cancer. In general a few things need to be considered, including selecting a biopsy site and obtaining an adequate sample for microscopic examination. Immunohistochemical and genetic analyses are necessary for confirmation of the diagnosis. Aggressive tissue biopsy for pathology study may increase the rate of diagnosis for double, or even triple primary malignancies. More precise diagnosis will provide more treatment choices. ***(Thorac Med 2017; 32: 142-149)***

Key words: metachronous primary malignancies, esophageal squamous cell carcinoma, small cell carcinoma

Introduction

The diagnosis of multiple primary malignant neoplasms (MPMN) in a patient has been reported rather frequently during the past decade. Although the mechanisms responsible for the development of MPMNs have yet to be fully explicated, some, including immune, hereditary and environmental factors, have been implicated in the pathogenesis of this entity [1-

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital, Kaohsiung Medical Center; **Graduate Institute of Clinical Medical Sciences, Chang Gung University College of Medicine, Taoyuan, Taiwan; ***Department of Respiratory Care, Chang Gung Institute of Technology, Chiayi, Taiwan, Republic of China

Address reprint requests to: Dr. Ying-Tang Fang, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital, Kaohsiung Medical Center, No. 123, Dapi Rd. Niaosong Dist, Kaohsiung City 83301 Taiwan, R.O.C.

2].

In a literature review of 1,104,269 cancer patients, the incidence of MPMN ranged from 0.73% to 11.7% [3]. With progress being made in diagnostic and biopsy techniques, the rate of diagnosis for double, and even triple primary malignancies increases year after year. Here, we present a patient with 3 metachronous primary malignancies, including cancer of the lung, left soft palate and esophagus.

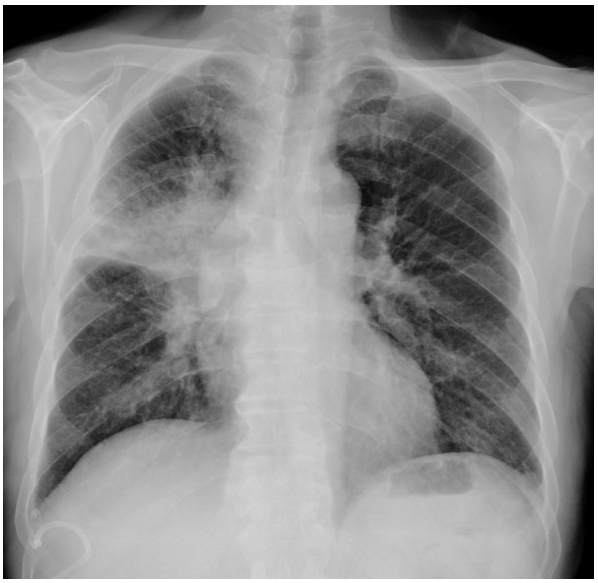
Case Report

A 63-year-old male who had been diagnosed as having esophageal squamous cell carcinoma (SCC) (T1N0Mx post-endoscopic submucosal dissection) in 2011 visited the ENT specialist clinic of Kaohsiung Chang Gung Memorial Hospital due to a left soft palate mass in 2012. A left soft palate tumor resection via flap uvulopalatopharyngoplasty was performed. The pathology results showed well-differentiated SCC (cT2N0M0). The patient's past and personal history included diabetes mellitus type 2, smoking (2-3 packs per day for more than 40 years), alcohol consumption (3 bottles per day for 20^{+} years) and betel nut chewing. The patient was followed up regularly in Kaohsiung Chang Gung Memorial Hospital (KCGMH) for both cancers. Serial follow-up image studies were arranged and showed no evidence of tumor recurrence or metastatic tumors.

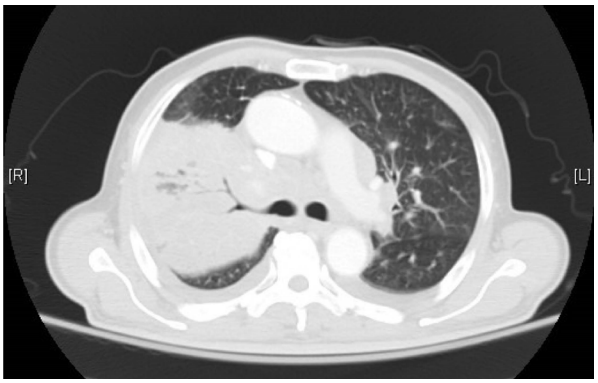
In 2014, the patient presented to KCGMH with blood-tinged sputum and progressive dyspnea. He had visited a local medical doctor first, where CXR showed right upper lobe (RUL) consolidation. Chest CT examination was arranged and revealed RUL consolidation with a suspicious 6 cm infiltrative mass invading the right hilum and mediastinum. In addition, bilateral pleural effusion and multiple liver nodules and masses (0.5-3.8 cm) in both lobes of the liver were noted in the chest CT image study (Figure 1). Brain MRI exam showed multiple metastatic nodules. Bone scan revealed that there were focal areas of moderately increased uptake in the occipital region of the skull, right border of T10, left anterior 6^{th} rib, and both proximal femoral shafts.

Bronchoscopy examination was performed and revealed mucosal irregularity at the right secondary carina, orifice of the RUL, right middle lobe and right lower lobe (Figure 2). Biopsy from the right secondary carina was performed and tissue samples were sent for pathologic study, which revealed small cell carcinoma of the bronchus. Bronchial mucosa with infiltrative nests, strands and sheets of small-sized neoplastic cells bearing hyperchromatic nuclei and scanty cytoplasm was noted in the microscopic pathologic findings. Immunohistochemical stain study showed positive results for AE1/AE3, TTF-1, CK7, and Ki-67 antibodies. Weakly positive synaptophysin and focally positive CD56 were noted (Figure 3), and T200, S100, P40 and chromogranin A were found to be negative. The immunohistochemical results were consistent with small cell carcinoma.

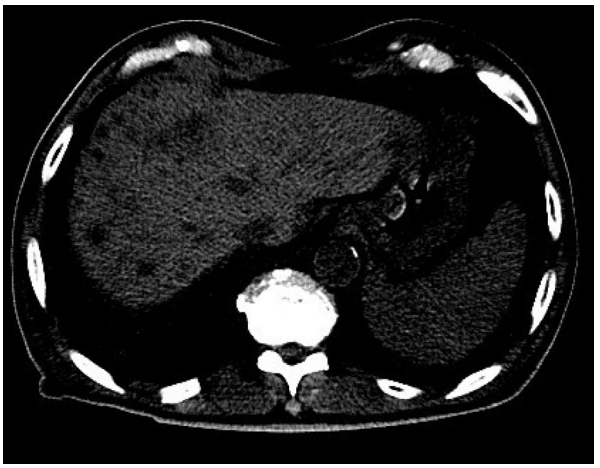
Echo-guided fine needle aspiration for right liver lobe tumor was performed and the pathology study showed metastatic small cell carcinoma. The immunohistochemical result was suggestive of a high-grade neuroendocrine carcinoma of the lung. Chemotherapy and radiotherapy were not performed due to the patient's poor performance status. The patient's condition worsened gradually, and on October 19. 2014, the family asked for the patient's discharge, against medical advice.



(A)



(B)



(C)

Fig 1. (A) CXR showed right upper lobe (RUL) consolidation; (B) chest CT revealed RUL consolidation with a suspicious 6 cm infiltrative mass invading the right hilum and mediastinum (partial encasement of the SVC and right lower tracheal wall); (C) CT revealed multiple liver nodules and masses (0.5-3.8 cm) in both lobes of the liver.

Discussion

Although the amount of research into MPMNs is increasing, its pathogenesis remains unclear. The most frequent factors involved are intense exposure to carcinogens, genetic susceptibility, the immune system of the patients, and the carcinogenic effects of radio/chemotherapy used in the treatment of tumors [1]. Increasing number of multiple independent malignant foci developing in the mucosa epithelium may be related to carcinogenic factors, such as tobacco

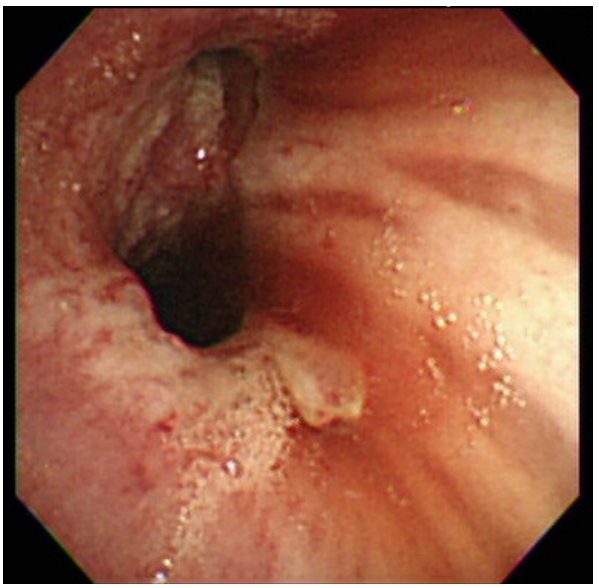
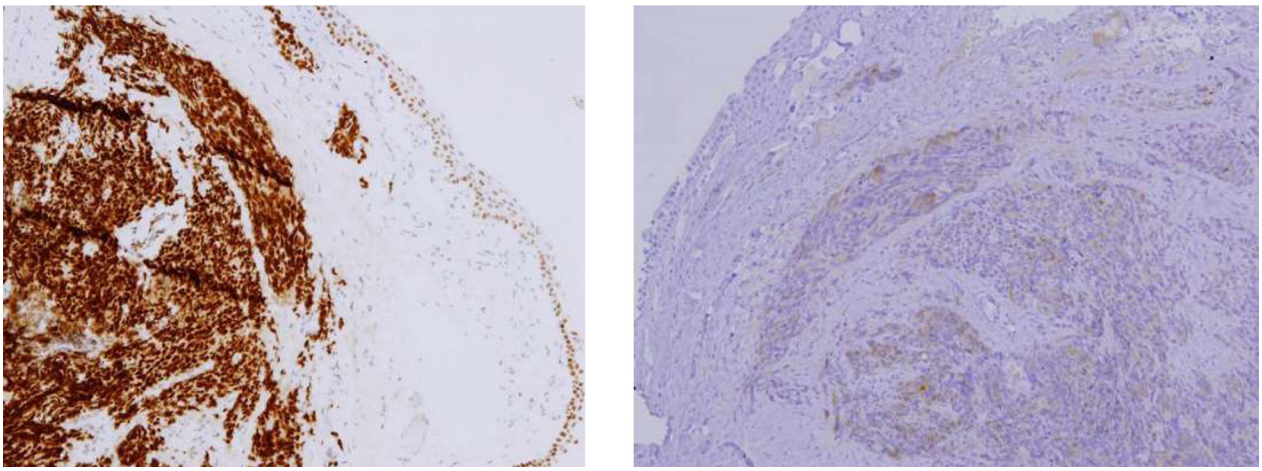


Fig 2. Mucosal irregularity at the right secondary carina, orifice of the RUL, RML and RLL



(A) (B)

Fig 3. (A) Immunohistochemical stain study of bronchus tissue showed a positive result for the antibody TTF-1 (Brown area). (B) Immunohistochemical stain study showed a positive result for the antibody synaptophysin.

and alcohol [4]. This phenomenon can be explained by the "field cancerization" concept, which was proposed by Slaughter *et al* in 1953. This concept describes extensive premalignant and malignant cytological changes that result in an increased risk of the development of multiple independent tumors [5].

The diagnosis of multiple primary cancers is based on the 3 criteria described by Warren and Gates [6]: First, neoplasms must be clearly malignant as determined by histological evaluation. Second, each neoplasm must be physically separate and distinct, with lesions usually being separated by normal-appearing mucosa. If a secondary neoplasm is contiguous to the initial primary tumour or is separated by mucosa with intraepithelial neoplastic change, the 2 should be considered as confluent growths, rather than multicentric carcinomas. The third criterion involves the recognition of the possibility that the secondary neoplasm represents a metastasis. The observation that the invasive carcinoma arises from an overlying epithelium that demonstrates a transition from carcinoma in situ to invasive carcinoma is helpful.

Depending on the time of diagnosis of each tumor, MPMNs are divided basically into 2 large categories: Synchronous tumors are those that are diagnosed simultaneously or within a 6-month interval. If the interval is longer than 6 months, the MPMNs are known as metachronous tumors [7-8].

In the present case, esophageal SCC (T1N0Mx post-endoscopic submucosal dissection) and left soft palate cancer (pT2N0M0 post tumor resection via flap uvulopalatopharyngoplasty) were diagnosed in 2011 and 2012 respectively. Endoscopy revealed the esophageal cancer lesion (32 cm from the incisors). Each of these 2 malignancies was physically separate, and the lesions were separated by normal-appearing mucosa. Serial follow-up image studies showed no evidence of tumor recurrence or metastatic tumors. The interval between the diagnosis of esophageal SCC and that of left soft palate malignancy was more than 6 months. The

interval between the diagnoses of left soft palate malignancy and lung small cell carcinoma was also more than 6 months. In other words, this patient was diagnosed with 3 metachronous primary malignancies.

Etiologic factors of esophageal squamous cell carcinoma

The incidence of esophageal SCC varies among different geographic regions. The highest rates are found in northern Iran, Central Asia, and north-central China (the so-called "esophageal cancer belt") [9]. A history of smoking, alcohol consumption, and diets low in fruits and vegetables were found to account for almost 90% of esophageal SCC in the United States [10]. Cigarette smoking is also a major risk factor in Asia, as smoking is common [11].

Relatively poor nutritional status, low intake of vegetables, chewing of betel nut and drinking beverages at high temperatures are also thought to be major risk factors for SCC in the "esophageal cancer belt" of Iran and Asia [12-16]. Other possible risk factors for esophageal SCC include prior gastrectomy, atrophic gastritis and human papillomavirus infection [17-19]. The etiologies of the 3 metachronous primary malignancies in this patient were most likely his history of smoking, alcohol consumption and betel nut chewing.

Pathobiology of small cell carcinoma of the lung

A diagnosis of small cell carcinoma of the lung (SCCL) is based primarily upon light microscopy [20]. For SCCL and large cell neuroendocrine carcinoma (LCNEC), there are standard immunohistochemical markers for lung origin and/or neuroendocrine features, which are useful for establishing the diagnosis. Virtually all SCCLs are immunoreactive for keratin and epithelial membrane antigen because of their epithelial cellular origin. A majority will also express thyroid transcription factor-1 (TTF-1), which can help distinguish SCCL from neuroendocrine cancers originating in an organ other than the lung. Markers reflecting neuroendocrine and neural differentiation commonly used for diagnosis include synaptophysin, chromogranin, and CD56 (neural cell adhesion molecule [NCAM]) [21-23].

Differential diagnosis of primary versus metastatic pulmonary malignancy

When pulmonary tumors are observed in patients with a history of cancer, the differentiation between metastasis and primary lung cancer plays a crucial role in decision-making. According to a summary of recommendations based on the American College of Chest Physicians (ACCP) Lung Cancer Guidelines, 3rd edition (LC III), a directed panel of immunohistochemical assays should be used to increase the diagnostic accuracy for individuals with lung tumors whose differential diagnosis includes primary lung carcinoma vs metastatic carcinoma (Grade 1C) [24].

In our case, invasive procedures, including bronchoscopy examination and echo-guided fine needle aspiration for the right liver lobe tumor, were performed to distinguish esophageal SCC with lung metastasis from primary lung cancer. Furthermore, microscopic and immunohistochemical stain studies were performed to confirm the site of primary tumor origin.

Conclusion

MPMNs seem to be diagnosed at a higher incidence than that predicted only by the influ-

ence of hazard. MPMN case studies can provide useful information regarding the development of effective screening and surveillance protocols, with the goal of treating patients effectively. Aggressive tissue biopsy for pathology study may also increase the rate of diagnosis for double, and even triple primary malignancies. More precise diagnoses will provide more treatment choices.

Acknowledgments

The authors thank all the physicians and research assistants from Kaohsiung Chang Gung Memorial Hospital who participated in this study.

References

1. Irimie A, Achimas-Cadariu P, Burz C, *et al*. Multiple primary malignancies: epidemiological analysis at a single tertiary institution. J Gastrointestin Liver Dis 2010; 19: 69-73.
2. Lynch CF, Hall P, Langmark F, *et al*. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. J Natl Cancer Inst 2007; 99: 1634-43.
3. Demandante CG, Troyer DA, Miles TP, *et al*. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. Am J Clin Oncol 2003; 26: 79-83.
4. Wang Y, Wu XT. Stomach carcinoma presenting with a synchronous liver cancer: a case report and literature review. Case Rep Gastrointest Med 2014; 2014: 970293
5. Mukaiyama Y, Suzuki M, Morikawa T, *et al*. Multiple primary malignant neoplasms of the glottis, renal pelvis, urinary bladder, oral floor, prostate, and esophagus in a Japanese male patient: a case report. World J Surg Oncol 2014; 12: 294.
6. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and statistical study. Am J Cancer 1932; 16: 1358-414.
7. Aydiner A, Karadeniz A, Uygun K, *et al*. Multiple primary neoplasms at a single institution: differences between synchronous and metachronous neoplasms. Am J Clin Oncol 2000; 23: 364-70.
8. Derwinger K, Gustavsson B. A study of aspects on gender and prognosis in synchronous colorectal cancer. Clin Med Insights Oncol 2011; 5: 259-64.
9. Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
10. He Z, Zhao Y, Guo C, *et al*. Prevalence and risk factors for esophageal squamous cell cancer and precursor lesions in Anyang, China: a population-based endoscopic survey. Br J Cancer 2010; 103: 1085-8.
11. Chen ZM, Xu Z, Collins R, *et al*. Early health effects of the emerging tobacco epidemic in China. A 16-year prospective study. JAMA 1997; 278: 1500-4.
12. Islami F, Ren JS, Taylor PR, *et al*. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. Br J Cancer 2009; 101: 1641-7.
13. Akhtar S, Sheikh AA, Qureshi HU, *et al*. Chewing areca nut, betel quid, oral snuff, cigarette smoking and the risk of oesophageal squamous-cell carcinoma in South Asians: a multicentre case-control study. Eur J Cancer 2012; 48: 655-61.
14. Islami F, Boffetta P, Ren JS, *et al*. High-temperature beverages and foods and esophageal cancer risk: a systematic review. Int J Cancer 2009; 125: 491-524.
15. Islami F, Pourshams A, Nasrollahzadeh D, *et al*. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. BMJ 2009; 338: b929.
16. Wu M, Liu AM, Kampman E, *et al*. Green tea drinking, high tea temperature and esophageal cancer in high- and low-risk areas of Jiangsu Province, China: a population-based case-control study. Int J Cancer 2009; 124: 1907-13.
17. Tachibana M, Abe S, Yoshimura H, *et al*. Squamous cell carcinoma of the esophagus after partial gastrectomy. Dysphagia 1995; 10: 49-52.
18. Islami F, Sheikhattari P, Ren JS, *et al*. Gastric atrophy and risk of oesophageal cancer and gastric cardia adenocarcinoma: a systematic review and meta-analysis. Ann Oncol 2011; 22: 754-60.
19. Li X, Gao C, Yang Y, *et al*. Systematic review with meta-analysis: the association between human papillomavirus infection and oesophageal cancer. Aliment Pharmacol Ther 2014; 39: 270-81.

20. Glisson, BS, Byers LA. Pathobiology of small cell carcinoma of the lung. In: UpToDate.
21. Ettinger DS, Aisner J. Changing face of small-cell lung cancer: real and artifact. J Clin Oncol 2006; 24: 4526-7.
22. Guinee DG Jr, Fishback NF, Koss MN, *et al*. The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. Am J Clin Pathol 1994; 102: 406-14.
23. Taneja TK, Sharma SK. Markers of small cell lung cancer. World J Surg Oncol 2004; 2: 10.
24. Detterbeck FC, Lewis SZ, Diekemper R, *et al*. Executive Summary Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2013; 143(5) (Suppl): 7S-37S.

三重異時性多原發惡性腫瘤：病例報告與文獻回顧

方映棠 * 黃國棟 * 王金洲 *,**,***

一位於西元 2011 診斷為食道鱗狀上皮細胞癌的 63 歲男性 (T1N0Mx 經內視鏡黏膜下切除) 於西元 2012 年因發現左軟顎腫塊前來就診，軟顎黏膜病理切片診斷為分化鱗狀上皮細胞癌。於西元 2014 年病患以咳血及漸進性呼吸困難為表現，前來高雄長庚紀念醫院求診。胸部 X 光片發現右上肺葉實質化，進一步的電腦斷層檢查發現右上肺葉腫塊合併多發性肝結節。本院為病患安排了支氣管鏡檢查合併腫瘤活檢切片，針對肝腫瘤則進行超音波導引細針穿刺術進行活檢切片，病理切片報告診斷為原發性肺小細胞癌合併肝轉移。針對疑似肺癌患者初始的評估診斷方法是基於先前非小細胞肺癌患者的研究結果。一般來說有幾件事情需要考慮，其中包括活檢部位的選擇，是否獲得足夠的鏡檢樣本。必要時免疫組織染色和遺傳分析是診斷確認的工具。針對病理切片檢查所採取的積極侵入性組織活檢可以提高雙重甚至三重原發惡性腫瘤的診斷率，更精確的診斷將提供更多的治療選擇。*(胸腔醫學 **2017; 32: 142-149**)*

關鍵詞：異時性多原發惡性腫瘤，食道鱗狀上皮細胞癌，小細胞癌

* 長庚醫療財團法人高雄長庚紀念醫院 內科部 胸腔科，** 長庚醫療財團法人長庚大學 臨床研究所
*** 長庚科技大學嘉義分部 呼吸照護系
索取抽印本請聯絡：方映棠醫師，長庚醫療財團法人高雄長庚紀念醫院 內科部 胸腔科，高雄市鳥松區大埤路 123 號

A Rare Case of Cold Abscess in the Anterior Chest Wall

Kai-Yu Hsiao*,**, Chung-Ping Hsu**, Ta-Wei Pu***, Chih-Hung Lin**

Primary tuberculous abscesses (also called “cold abscesses”) of the chest wall are rare and constitute less than 10% of skeletal extrapulmonary tuberculosis cases. Tuberculosis of the chest wall usually presents as an enlarged and occasionally painful mass in the chest wall. Cases of tuberculous abscess of the anterior chest wall are rarely reported in the literature. We reported a rare case of tuberculous abscess of the anterior chest wall in a 64-year-old man who presented with painful swelling in the left chest region. Physical, imaging, and histological examinations led to a diagnosis of tuberculous chest wall lesion. Complete excision of the cold abscess and partial resection of the left 6th rib were performed. During surgery, 150 mL of purulent fluid was found in the cyst. The patient was stable postoperatively and received anti-tuberculosis medication. Cold abscess of the anterior chest wall is difficult to diagnose preoperatively and may be confused with secondary bone metastasis, pyogenic abscess, chondroma, multiple myeloma, lymphoma, or infectious diseases such as actinomycosis. Complete excision of the abscess of the chest wall and of the invaded structures is our preferred approach to achieve *en bloc* resection. When a chest wall tumor with a cystic lesion and homogenous fluid content is encountered, cold abscess should be suspected. ***(Thorac Med 2017; 32: 150-156)***

Key words: tuberculosis, cold abscess, chest wall

Introduction

Chest wall tuberculosis (TB), also called cold abscess, is the rare localization of extrapulmonary TB and comprises less than 10% of skeletal TB cases [1-3]. Three mechanisms are suggested in the pathogenesis of a tuberculous abscess of the chest wall: direct invasion from underlying pleural or pulmonary lesions, local extension from lymphadenitis of the chest wall, and hematogeneous dissemination [4-5]. Tuberculous abscess of the anterior chest wall is difficult to diagnose preoperatively because the lesions grossly simulate pyogenic abscess or tumor. We report a case of tuberculous abscess of the chest wall in a 64-year-old man, for which

*Division of Thoracic Surgery, Department of Surgery, Taichung Armed Forces General Hospital, National Defense Medical Center, Taichung, Taiwan; **Division of Thoracic Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan; ***Division of Colon and Rectal Surgery, Department of Surgery, Songshan Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
Address reprint requests to: Dr. Chung-Ping Hsu, Division of Thoracic Surgery, Department of Surgery, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sect. 4, Taichung, Taiwan 40705, ROC

we performed complete abscess excision with partial rib resection, followed by postoperative anti-TB therapy.

Case Report

A previously healthy 64-year-old man presented to our hospital's outpatient department with painful swelling in the left chest region over the 5th to 7th ribs. He reported that the swelling had gradually increased during a 2-month period. The patient had no history of previous surgery or trauma. He had no pulmonary symptoms, such as productive cough, fever, or hemoptysis, or other symptoms. On physical examination, body temperature and vital signs were all within normal ranges. A chest examination revealed 2 palpable (3×3 cm and 5×3 cm in size, respectively), soft, tender, and mobile fluctuating masses. The lesions were unattached to underlying structures. Laboratory data indicated a white cell count of 6.96×10^3/μL, with a neutrophil count of 68.6%, and a lymphocyte count of 22.3%. Serum electrolytes, thyroid function tests, and liver and renal function tests were within normal ranges. HIV antibodies, anti-hepatitis B surface antigen, and anti-hepatitis C virus were non-reactive. Chest radiography revealed fibronodules at bilateral upper lobes (Figure 1). Contrast-enhanced computed tomography (CT) of the thorax revealed 2 homogenous hypodense lesions located between the serratus anterior and intercostal muscles, from the 5th to 6th intercostal (ICS) region, adjacent to the costal cartilage, with destruction of the left 6th rib (Figure 2). These findings were suggestive of primary chest wall tumor with central necrosis, secondary metastatic tumor, or an infective process like TB; thus, we conducted a magnetic resonance imaging (MRI) examination of the thorax for further evaluation. Contrast-enhanced MRI revealed the presence of a multilobulated fluid collection with marginal contrast enhancement of the subcutaneous tissue, deep fasciae, and muscle layer of the anterior-inferior quadrant of the chest wall, approximately 11.5×7.5×2.5 cm in size. Ill-defined edema and contrast enhancement were noted in the surrounding tissue. The findings were indicative of an infectious process with abscess formation. Pyo-myofascitis with abscess formation or TB of the chest wall was suspected (Figure 3).

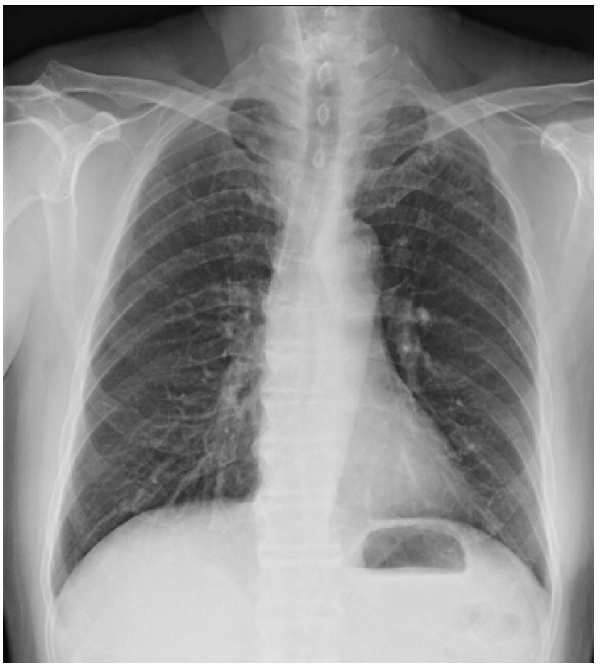
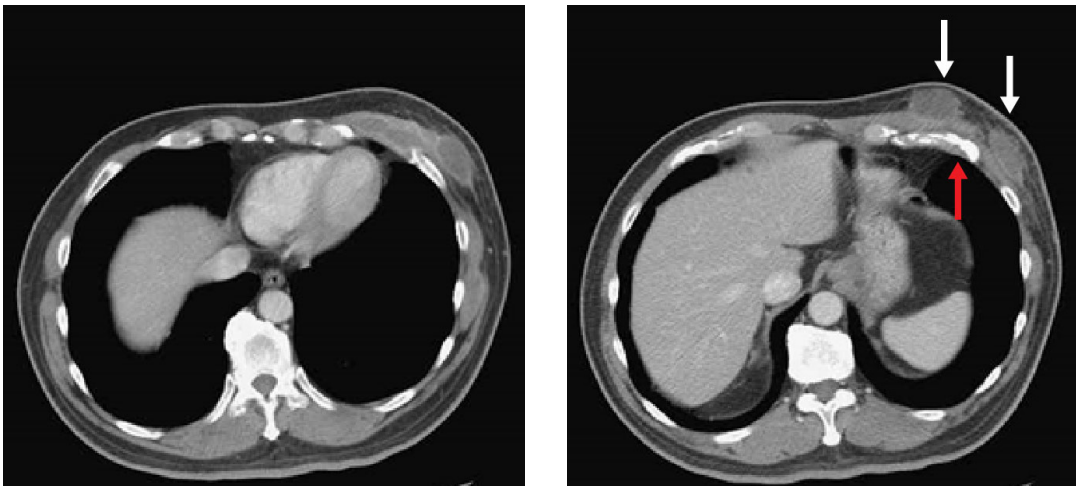


Fig. 1. Chest radiograph

We performed complete tumor excision with partial resection of the 6th rib. Intraoperative findings were as follows: 1) a dumbbell-shaped cystic tumor, about 12×6×4 cm in size, was found in the anterior portion of the left 5th intercostal space with invasion of the 6th rib. The tumor content was a yellowish pus-like turbid fluid, with a volume of approximately 150



(A) (B)

Fig. 2. Chest contrast-enhanced computed tomography scan. (A) Two homogenous hypodense lesions (white arrow) located in the left 5th - 6th intercostal region. (B) Tumor invasion to the left 6th rib with bony destruction (red arrow).

mL. 2) The parietal pleura was intact without tumor invasion (Figure 4A, 4B).

Histologic examination revealed fibroconnective tissue with necrotizing granulomatous inflammation. Special stains for periodic acid-Schiff and acid-fast staining were utilized and acid-fast bacilli were found (Figure 5); this result was further confirmed by Amplicor polymerase chain reaction (PCR) assay and TB culture. We consulted a chest medicine specialist, who arranged further anti-TB treatment for 9 months post-operation.

Discussion

Primary tuberculous abscesses of the chest wall are rare and constitute less than 10% of skeletal TB [1-3]. Tuberculous abscess of the chest wall usually presents as an enlarged and occasionally painful mass on the chest wall [6]. A review of the literature suggests 3 mechanisms in the pathogenesis of tuberculous abscess of the chest wall: 1) direct invasion from underlying pleural or pulmonary lesions, 2) local extension from lymphadenitis of the chest wall, and 3) hematogenous dissemination [4-5].

Diagnosing primary TB of the chest wall preoperatively is often challenging, and diagnosis is often by postoperative pathologic examination [7]. The differential diagnoses include secondary bone metastasis, pyogenic abscess, chondroma, multiple myeloma, lymphoma, or infectious disease such as actinomycosis. Primary tuberculous abscesses of the chest wall may be confirmed by acid-fast staining, PCR, or culture of the abscess obtained by needle aspiration. However, needle aspiration diagnosis of a tuberculous abscess is not as reliable as the other methods, since it has a diagnostic accuracy of only 36.3%. Some authors recommend surgical biopsy [7-8].

About 70-80% of patients with tuberculous abscesses of the chest wall have a past history of TB infection, and 20-60% of these patients have active TB [3-4]. Nevertheless, patients without a definite history of TB or concurrent

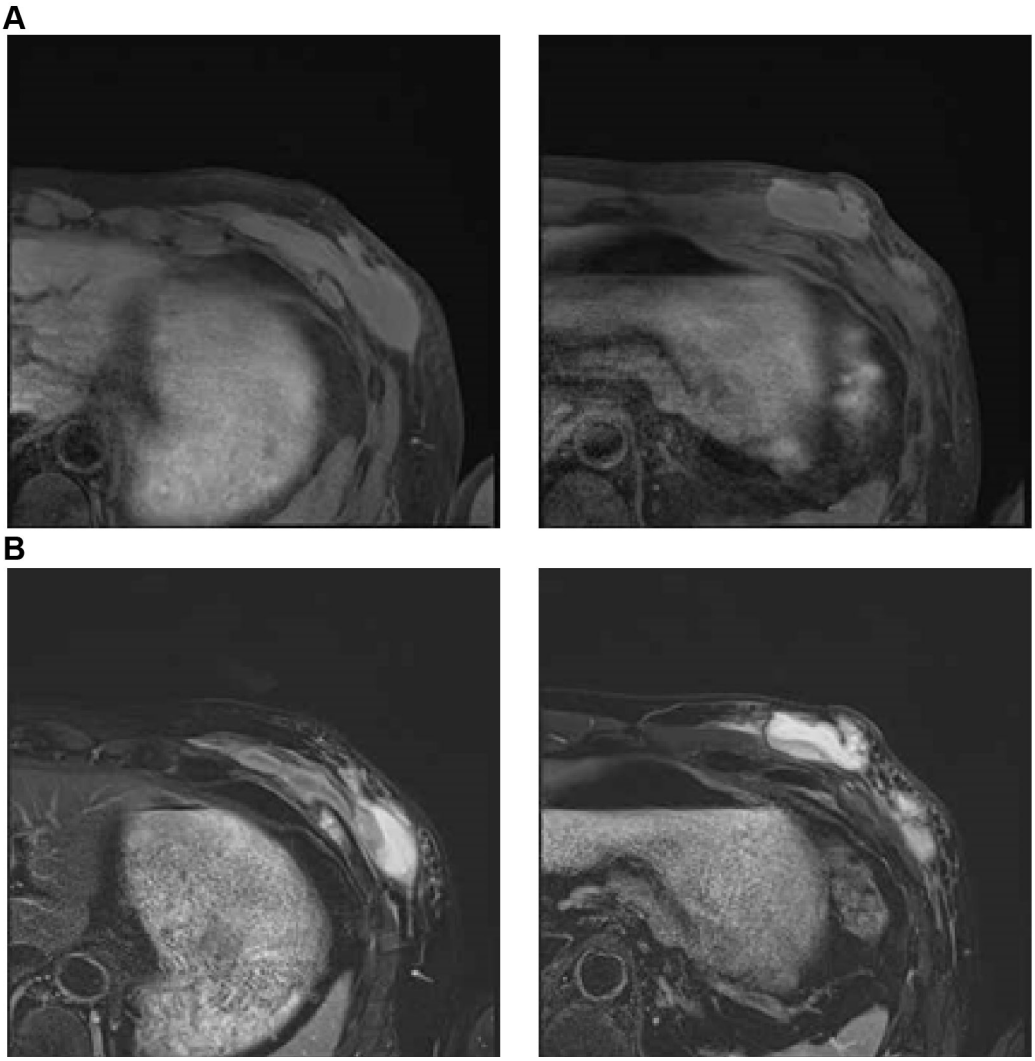
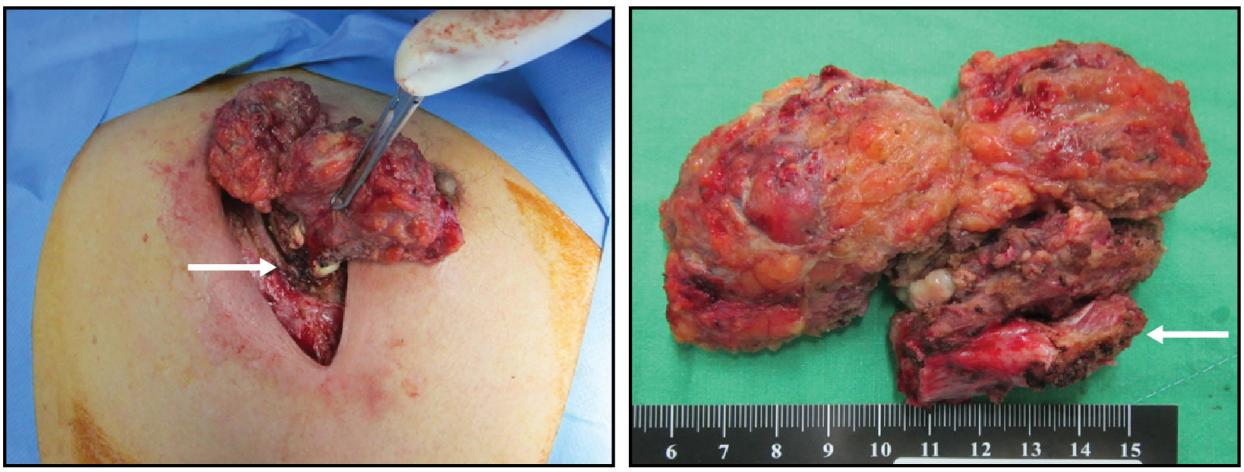


Fig. 3. Magnetic resonance imaging (MRI). (A) T1-Turbo Spin Echo, fat-saturated, axial MRI. (B) T2-BLADE with fat-saturated axial MRI. Presence of multilobulated fluid collection with marginal contrast enhancement in the subcutaneous tissue, deep fasciae, and muscle layer of the anterior-inferior quadrant of the chest wall, approximately 11.5×7.5×2.5 cm. Ill-defined edema and contrast enhancement are noticeable in the surrounding tissue.

active TB still can have fresh tuberculous abscess of the chest wall, as in our case.

Tuberculous abscesses of the chest wall can involve the costochondral junctions, sternum, ribs shafts, costovertebral joints, and the vertebrae. They often occur as solitary lesions, but are found in 2 or more sites in some patients. In our case, 2 tuberculous lesions of the chest wall were found. These lesions frequently occur at the margins of the sternum and in the shafts of the ribs [8]. Our case involved a tuberculous abscess that extended along the intercostal muscles alone, with the destruction of the 6th rib.

Patients should undergo chest CT to evaluate the extent of abscess cavities and the status of the ribs, sternum, cartilage, and pleural space. The functional status of the lung parenchyma and thoracic cavities may also be evalu-



(A) (B)

Fig. 4. (A) Intraoperative photography. Left anterior thoracotomy and dissection to the intercostal space level. Invasion of the sixth rib (arrow) was noted. (B) Specimen. A dumbbell-shaped cystic tumor, approximately 12×6×4 cm in size at the anterior portion of the left 5th intercostal space, with invasion of the 6th rib (arrow).

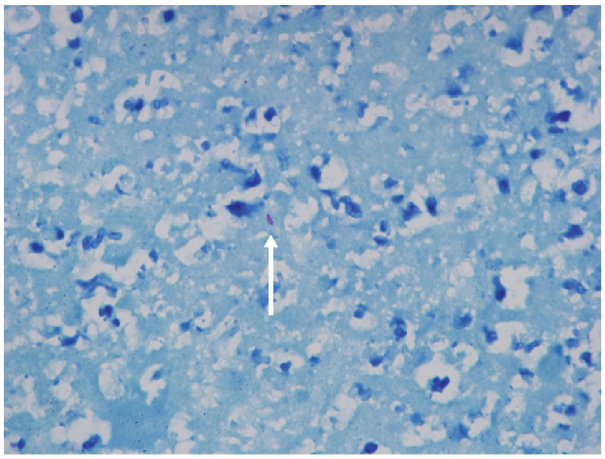


Fig. 5. *Mycobacterium tuberculosis* (white arrow), acid-fast staining.

ated to exclude other inflammatory or tumor lesions [9]. A common CT finding in tuberculous abscess is a low density of the central area with rim enhancement of the peripheral area [10].

Many diseases that affect the chest wall have unique CT or MRI characteristics that differentiate them from other diseases. CT may reveal bony involvement with higher sensitivity and specificity when compared to MRI or ultrasound, which would have a significant impact on the differential diagnoses of these conditions [11].

The definitive treatment for chest wall TB has not yet been determined. Some studies have reported frequent recurrence after anti-TB medication only [8,12]. Some reports recommend a combination of anti-TB medication and surgical management to reduce recurrence [7]. Aggressive debridement with primary closure and postoperative medical treatment is required to prevent recurrence or draining sinus formation [13].

The best methods of surgical treatment are still undetermined. Kim *et al*. classified surgical methods into debridement and drainage alone, and complete resection with or without skeletal resection. Their study reported a 40% recurrence rate in the debridement and drainage group compared to the complete resection group (9.2%). Cold abscess of the chest wall should be treated using complete resection of all the involved areas in addition to the ap-

propriate anti-TB chemotherapy [1]. Paik *et al*. reported a 16% recurrence rate in patients who underwent debridement and drainage, but only a 1.6% recurrence rate in the group with complete resection with rib resection [14]. We suggest that wide and complete resection would decrease recurrence. In our case, we performed a complete resection of the abscess with rib resection.

Conclusion

TB infection usually involves the lungs and the hilar lymph nodes. Cold abscess of the anterior chest wall is hard to diagnose preoperatively and may appear similar to secondary bone metastasis, pyogenic abscess, chondroma, multiple myeloma, lymphoma, or infectious disease such as actinomycosis. Complete excision of the tuberculous chest wall abscess and invasive structure is our preferred approach to achieve *en bloc* resection. Adequate postoperative anti-TB medication may reduce the chance of recurrence. When a chest wall tumor with cystic lesion and homogenous fluid content is encountered, cold abscess should be suspected.

References

1. Kim YT, Han KN, Kang CH, *et al*. Complete resection is mandatory for tubercular cold abscess of the chest wall. Ann Thorac Surg 2008; 85: 273-7.
2. Kuzucu A, Soysal O, Günen H. The role of surgery in chest wall tuberculosis. Interact Cardiovasc Thorac Surg 2004; 3: 99-103.
3. Cho KD, Cho DG, Jo MS, *et al*. Current surgical therapy for patients with tuberculous abscess of the chest wall. Ann Thorac Surg 2006; 81: 1220-6.
4. Hsu HS, Wang LS, Wu YC, *et al*. Management of primary chest wall tuberculosis. Scand J Thorac Cardiovasc Surg 1995; 29: 119-23.
5. Tanaka S, Aoki M, Nakanishi T, *et al*. Retrospective case series analysing the clinical data and treatment options of patients with a tubercular abscess of the chest wall. Interact Cardiovasc Thorac Surg 2012; 14: 249-52.
6. Meade RH, Jr. Localized tuberculosis of the chest wall. Ann Surg 1933; 97: 247-58.
7. Keum DY, Kim JB, Park CK. Surgical treatment of a tuberculous abscess of the chest wall. Korean J Thorac Cardiovasc Surg 2012; 45: 177-82.
8. Faure E, Souilamas R, Riquet M, *et al*. Cold abscess of the chest wall: a surgical entity? Ann Thorac Surg 1998; 66: 1174-8.
9. Lee G, Im JG, Kim JS, *et al*. Tuberculosis of the ribs: CT appearance. J Comput Assist Tomogr 1993; 17: 363-6.
10. Morris BS, Maheshwari M, Chalwa A. Chest wall tuberculosis: a review of CT appearances. Br J Radiol 2004; 77: 449-57.
11. Jeung MY, Gangi A, Gasser B, *et al*. Imaging of chest wall disorders. Radiographics 1999; 19: 617-37.
12. Sakuraba M, Sagara Y, Komatsu H. Surgical treatment of tuberculous abscess in the chest wall. Ann Thorac Surg 2005; 79: 964-7.
13. Sonhaye L, Amadou A, Gnandi-Piou F, *et al*. Tuberculous abscess of the chest wall simulates pyogenic abscess. Case Rep Radiol 2015; 2015: 195412.
14. Paik HC, Chung KY, Kang JH, *et al*. Surgical treatment of tuberculous cold abscess of the chest wall. Yonsei Med J 2002; 43: 309-14.

罕見的前胸壁冷膿瘍

蕭凱宇 *,** 徐中平 ** 浦大維 *** 林志鴻 **

胸壁的肺外結核感染是個罕見的侵犯區域，臨床上常常以逐漸長大的胸壁腫瘤或者胸痛來表現，但是之前的文獻記載對於肋骨的肺外結核感染並不多見。

我們報告一個不常見的胸壁冷膿瘍的病例，包含病人臨床症狀、安排檢查的思路邏輯、後續的影像發現及手術切除的預後。胸壁冷膿瘍是個難以在影像學上診斷的疾病，與一般的細菌感染、放射菌感染、軟骨瘤、淋巴瘤、多發性骨髓瘤、骨轉移性腫瘤皆有相似的地方。完整的手術切除加上後續的抗結核菌藥物治療是我們推薦的選擇。因此外科醫師要把胸壁冷膿瘍列為一個鑑別診斷，才能給病人最適當的治療。
*(胸腔醫學 **2017; 32: 150-156**)*

關鍵詞：肺外結核，胸壁，冷膿瘍

* 國軍台中總醫院　外科部　胸腔外科，** 台中榮民總醫院　外科部　胸腔外科
*** 三軍總醫院松山分院　外科部　大腸直腸外科
索取抽印本請聯絡：徐中平醫師，台中榮民總醫院　外科部　胸腔外科，407 台中市西屯區台灣大道四段 1650 號