ISSN 1023－9855

胸腔醫學

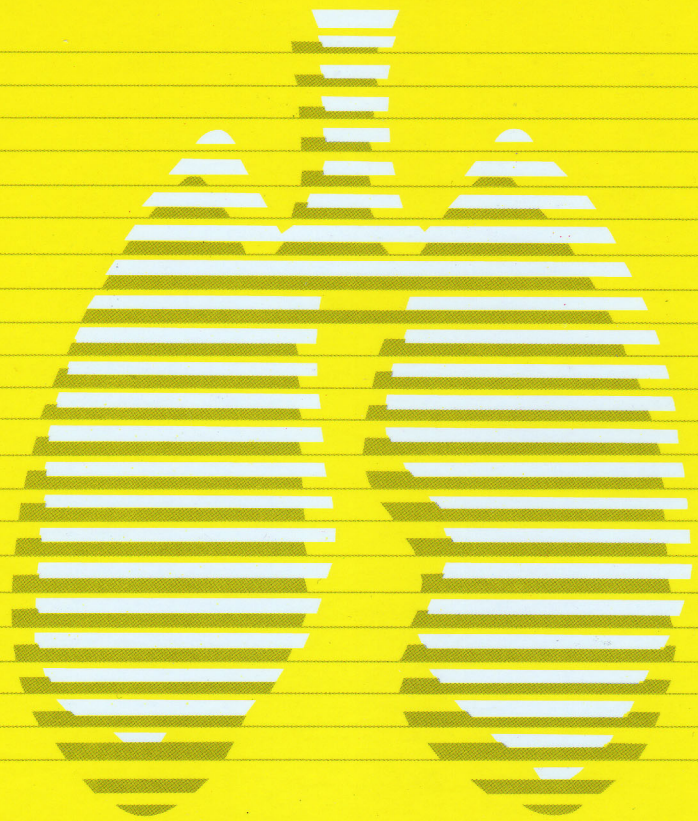
Thoracic Medicine

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

Vol.29 No.4 August 2014

第二十九卷 第四期

中華民國一〇三年八月



台灣胸腔暨重症加護醫學會

11217 台北市北投區石牌路二段201號

5.No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan 11217, R.O.C.

ISSN 1023－9855

中華民國一〇三年八月　第二十九卷　第四期
ISSN 1023－9855
Vol.29 No.4 August 2014

胸腔醫學
Thoracic Medicine

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

原著

病例報告

中華民國一〇三年八月　第二十九卷　第四期

ISSN 1023－9855

胸腔醫學
Thoracic Medicine

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

Vol.29 No.4 August 2014

Orginial Articles

Case Reports

Prognostic Value of Chemo-Naïve Serum Carcinoembryonic Antigen Level in Patients with Non-Small-Cell Lung Cancer

Hsu-Ching Kao*, Huang-Chih Chang*, Meng-Chih Lin*,**, Wen-Feng Fang*,**, Kuo-Tung Huang*, Chia-Chen Tseng*, Shih-Feng Liu*,**, Chin-Chou Wang*,**

Background: Carcinoembryonic antigen (CEA) is a known marker for non-small cell lung cancer (NSCLC) and was suggested as a risk factor for mortality and poor prognosis in some studies of a small sample size involving patients in early and advanced stages of NSCLC. The aim of this study was to assess the prognostic value of the serum CEA level in a larger chemo-naïve patient population with NSCLC of different stages.

Methods: Two hundred fifty-one (251) patients with stage II to IV NSCLC had their serum CEA measured before chemotherapy, and then received cisplatin and gemcitabine as first-line chemotherapy at Kaohsiung Chang Gung Memorial Hospital from 2008/01 to 2011/12. Patients were subdivided into 2 groups: pre-chemotherapy serum CEA level ≥40 ng/ml and <40 ng/ml. We analyzed the difference in clinical characteristics, overall survival, and 2-year mortality between the 2 groups. We also examined the association between the serum CEA level and the sites of metastasis.

Results: Of the 251 patients with NSCLC, 183 (72.9%) had a serum CEA level <40 ng/mL and 68 (27.1%) had a CEA level ≥40 ng/mL. Univariate analysis showed adenocarcinoma (p=0.014), advanced staging (p=0.007), and metastasis (p=0.037) were associated with CEA ≥40 ng/ml. Multivariate Cox regression analysis showed that performance status (AHR 3.49; 95% CI, 1.81-6.72; p=0.000), staging (AHR 5.37; 95% CI, 1.94-14.82; p=0.001) and age ≥70 (AHR 1.84; 95% CI, 1.02-3.24; p=0.044) were prognostic factors for mortality in patients with NSCLC. The serum CEA level was not a prognostic factor for mortality, nor did it predict the site of metastasis in patients with stage IIIb NSCLC.

Conclusions: Serum CEA level was not a prognostic factor for mortality in patients with NSCLC in our study. ***(Thorac Med 2014; 29: 200-208)***

Key words: non-small cell lung cancer, carcinoembryonic antigen (CEA), mortality, predictor

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung 833, Taiwan
**Department of Respiratory Therapy, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung 833, Taiwan
Hsu-Ching Kao and Huang-Chih Chang contributed equally to the work for this study as first anthors.
Address reprint requests to: Dr. Chin-Chou Wang, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No. 123 Dabi Road, Niaosung, Kaohsiung, Taiwan

Introduction

Lung cancer is the most common cancer worldwide, with an estimated 1.6 million new cases and 1.38 million deaths in 2008 [1]. Carcinoembryonic antigen (CEA) is a glycosyl phosphatidyl inositol (GPI)-cell surface anchored glycoprotein whose specialized sialofucosylated glycoforms serve as functional colon carcinoma L-selectin and E-selectin ligands. The role of CEA as a diagnostic and prognostic marker has been extensively studied in different cancers, but its role as a prognostic marker in lung cancer is still widely debated. A recent review article [2] summarized studies on the role of CEA in lung cancer published in the last 30 years. They found 23 studies investigating the use of the CEA serum level as a prognostic marker in non-small cell lung cancer (NSCLC), and 2 studies investigating the use of the CEA plasma level in NSCLC. In 18 of these studies CEA was found to be a useful prognostic marker for either overall survival (OS), recurrence after surgery or/and progression free survival (PFS) in NSCLC patients. However, most of these studies focused on early-stage disease or pre-operation in adenocarcinoma patients. Thus, the role of CEA as a prognostic marker in NSCLC is still unclear, especially at more advanced stages. Therefore, the aim of our study was to investigate the prognostic value of the serum CEA level in patients with stage II to IV NSCLC before receiving chemotherapy.

Material and Methods

Patients and study design

The records of 251 consecutive patients with newly diagnosed NSCLC at clinical stage II to IV were retrospectively studied. The study period was from January 2008 to December 2011 at Kaohsiung Chang Gung Memorial Hospital in Taiwan. All patients had serum CEA measured prior to chemotherapy, and subsequently received cisplatin and gemcitabine as first-line chemotherapy. The clinical investigation section of our hospital measured serum CEA levels using the 2-site immunoenzymometric assay; the normal upper limit for this assay was 5 ng/mL.

Other data retrieved from the hospital's records included the patient's age, gender, smoking history, cancer histological classification, cancer staging, performance status (PS) (according to the Eastern Cooperative Oncologic Group scale, ECOG), and sites of cancer metastasis. The diagnosis of NSCLC was established histopathologically in accordance with the WHO classification [3]. Staging was performed in accordance with the TNM classification [4]. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and the requirements for patient consent were waived

Adenocarcinoma was present in 138 (55%) patients, squamous cell carcinoma in 44 (18%), and adenosquamous, bronchia-alveolar cell carcinoma or NCSLC not otherwise specified (NOS) in 69 (27%) patients. Stage II to IIIA disease was observed in 64 (25%) patients, and stage IIIB and IV in 187 (75%) patients. Patients were subdivided into 2 groups: pre-chemotherapy serum CEA level ≥40 ng/ml and <40 ng/ml. The cutoff value for serum CEA chosen in our study was 40 ng/mL, based on the result of a previous study [5] showing that basal CEA serum levels ≥40 ng/mL were associated with adenocarcinoma histological type and presence of CNS metastasis at diagnosis, but not with age, gender, positive smoking history, or other

patient characteristics. The primary outcomes of our study were OS and mortality within 2 years of the diagnosis of lung cancer. Correlations between CEA levels and sites of metastasis in stage IIIB patients were also analyzed.

Statistical analysis

Categorical variables were analyzed using the chi-square test or Fisher's exact test where appropriate, and continuous variables were compared using Student's *t*-test or the Mann-Whitney *U* test. OS was calculated as the period from the diagnosis of malignancy until death from any cause or until the date of the last follow-up visit for patients still alive. Living patients were censored at the time of the last follow-up. The OS and 95% confidence intervals (CI) were calculated using the Kaplan-Meier method. Multivariate Cox regression analysis was performed to identify independent risk factors associated with 2-year mortality.

Results

Patient characteristics

One hundred eighty-three (72.9%) of the 251 patients had CEA levels less than 40 ng/mL (the low CEA group), and the remaining 68 patients (27.1%) had CEA levels greater than 40 ng/mL (the high CEA group). Several differences between the 2 groups were noted. First, although adenocarcinoma was the most common histological type of lung cancer in both groups, it was more commonly seen in the high CEA group (67.6% versus 50.3%, p=0.014). Second, there was a larger proportion of patients with squamous cell carcinoma in the low CEA group than in the high CEA group (22.4% versus 4.4%, p=0.001). There was no significant difference between the 2 groups with regard to the other histological types. Third, the TNM stage of lung cancer was also significantly different between the 2 groups. More patients in the high CEA group were at stage IIIB and IV disease than in the low CEA group (86.6% versus 69.9%, p=0.007). Fourth, when the state of metastasis of lung cancer was analyzed, it was found that metastasis (including both M1a and M1b disease) was more common in the high CEA group (75.4% versus 59.9%, p=0.037). There was no significant difference between the 2 groups in terms of age, gender, smoking history, and PS (Table 1).

Overall survival and 2-year mortality

Using the Kaplan-Meier model, factors associated with lower OS included age ≥70 years (p<0.001), male gender (p<0.001), smoker (p<0.001), squamous cell carcinoma (p=0.008), PS ≥3 (p<0.001), advanced disease stage (IIIB and IV) (p<0.001), and CEA level ≥40 ng/mL (p=0.007). When multivariate Cox regression analysis was performed, PS ≥3 (AHR 3.49; 95% CI, 1.81-6.72; p<0.001), stage IIIB or IV disease (AHR 5.37; 95% CI, 1.94-14.82; p=0.001) and age >70 years (AHR 1.84; 95% CI, 1.02-3.24; p=0.044) were found to be prognostic factors for 2-year mortality. However, CEA level was not a prognostic factor for 2-year mortality in this study (Table 2).

CEA and site of metastasis

There was no significant difference in the relationship between site of metastasis and level of CEA in stage IIIB NSCLC patients (Table 3).

Discussion

Adenocarcinoma is the most common type of lung cancer in contemporary series, account-

Table 1. The Characteristics of Patients with NSCLC* Associated with CEA* >40 and <40 ng/ml+

	Total	Univariate analysis		*p* value
		CEA <40 (N=183)	CEA ≥40 (N=68)	
Age				0.828
-<70	143	104 (56.8%)	39 (57.4%)	
-≥70	98	79 (43.2%)	29 (42.6%)	
Gender				0.1
-Male	121	94 (51.4%)	27 (39.7%)	
-Female	130	89 (48.6%)	41 (60.3%)	
Smoke				0.15
-Non smoking	154	106 (57.9%)	48 (70.6%)	
-Smoking	95	75 (41.0%)	20 (29.4%)	
Histology				0.003
-Adenocarcinoma	138	92 (50.3%)	46 (67.6%)	0.014
-SCC*	44	41 (22.4%)	3 (4.4%)	0.001
-other	69	50 (27.3%)	19 (27.9%)	0.922
Performance Status				0.136
-<3	199	149 (86.1%)	50 (78.1%)	
-≥3	38	24 (13.9%)	14 (21.9%)	
Stage				0.007
-<3B	64	55 (30.1%)	9 (13.2%)	
-≥3B	187	128 (69.9%)	59 (86.6%)	
T				0.536
-1	17	15 (9.2%)	2 (3.5%)	
-2	87	65 (39.9%)	22 (38.6%)	
-3	32	23 (14.1%)	9 (15.8%)	
-4	84	60 (36.8%)	24 (46.1%)	
N				0.253
-0	41	35 (32.1%)	6 (16.2%)	
-1	35	23 (16.8%)	12 (25.5%)	
-2	70	51 (37.2%)	19 (40.4%)	
-3	38	28 (20.4%)	10 (21.3%)	
M				0.037
-0	75	61 (40.1%)	14 (24.6%)	
-1	134	91 (59.9%)	43 (75.4%)	

* NSCLC: Non-small cell lung cancer; CEA: Carcinoembryonic antigen; SCC: Squamous cell carcinoma

+ Categorical variables were analyzed by chi-square test and expressed as number (percentage)

Table 2. Independent Predictors Associated with Overall Survival in Patients with Advanced NSCLC*+

	Kaplan Meier analysis		Cox regression analysis	
	OS Mean±SE (months)	*p* value	AHR (95% CI)	*p* value
Age		0.000	1.84 (1.02-3.24)	0.044
-<70	39.05±2.93			
-≥70	23.91±3.51			
Gender		0.000		
-Male	28.77±2.57			
-Female	42.49±2.71			
Smoke		0.000		
-Non smoking	41.87±2.50			
-Smoking	25.71±2.73			
Histology		0.023		
-Adenocarcinoma	38.47±2.58	0.063		
-SCC*	25.14±3.84	0.008		
-other	36.15±3.69	0.951		
Performance Status		0.000	3.49 (1.81-6.72)	0.000
-<3	40.25±2.15			
-≥3	11.00±1.96			
Stage		0.000	5.37 (1.94-14.82)	0.001
-<3B	52.23±3.57			
-≥3B	29.99±2.10			
T		0.002		
-1	55.82±6.58	0.015		
-2	34.54±2.83	0.697		
-3	45.43±5.27	0.102		
-4	26.54±2.66	0.001		
N		0.006		
-0	52.69±4.47	0.003		
-1	37.24±5.03	0.883		
-2	30.36±3.03	0.106		
-3	30.35±4.69	0.052		
M		0.002		
-0	44.35±3.54			
-1	28.11±2.19			
CEA*		0.007		
-<40	39.11±2.32			
-≥40	25.10±2.72			

* NSCLC: Non-small cell lung cancer; CEA: Carcinoembryonic antigen; SCC: Squamous cell carcinoma

+ Categorical variables were analyzed by chi-square test and expressed as number (percentage)

Table 3. The Relationship between Serum CEA* Level and Site of Metastasis in Patients with Stage III b of NSCLC*+, and Time to Metastasis‡

	CEA <40 N=89 (78.1%)	CEA ≥40 N=25 (21.9%)	*p* value
No metastatis*	18 (20.2%)	4 (16.0%)	0.636
Brain metastasis	16 (18%)	2 (8%)	0.227
	505±324	382	0.382
Bone metastasis	23 (25.8%)	7 (28.0%)	0.829
	304±254	507±274	0.406
Liver metastasis	5 (5.6%)	3 (12.0%)	0.270
	686±379	289±288	0.333
Lung metastasis	2 (2.2%)	1 (4.0%)	0.629
	149±106	210	0.223
Other metastasis	25 (28.1%)	8 (32.0%)	0.703
	535±473	293±260	0.491
overall	432±386	354±243	0.354

* NSCLC: CEA: Carcinoembryonic antigen; Non-small cell lung cancer

+ Categorical variables were analyzed by chi-square test and are expressed as number (percentage)

‡ Time to metastasis were expressed as Days, mean±SD

ing for more than one-half of lung cancer cases [1]. Our study reflected the current trend, with the majority of the NSCLC cases in our study (55%) being adenocarcinoma. CEA is a well-known marker for NSCLC, especially for adenocarcinoma. Our study result revealed that adenocarcinoma was the most common lung cancer cell type in both groups (67.6% in the high CEA group, 50.3% in the low CEA group). Only 22.4% of cancers in the low CEA group and 4.4% in the high CEA group were squamous cell carcinoma, indicating CEA is a better marker for adenocarcinoma than for squamous cell carcinoma. This phenomenon is useful for the differential diagnosis of NSCLC, especially in clinical situations with patients with highly suspected lung cancer for whom invasive procedures such as bronchoscopic biopsy or open lung biopsy are not feasible. However, elevated serum concentrations of CEA were also found in various benign pathologies and other malignancies, which precluded its use in screening.

Our study revealed a high CEA level was associated with more advanced disease. This is consistent with the results of previous studies in which CEA correlated with tumor size, tumor burden and cancer stage [6-7]. Our result also showed that high CEA levels were correlated with the risk of metastasis. Evidence has also shown that serum CEA levels produced by malignant cells can enhance the metastatic potential of otherwise weakly metastatic cells [8-11]. It was hypothesized that CEA may function as an attachment factor for cancer cells [11]. However, pre-chemotherapy serum CEA levels were not correlated with specific sites of distant metastasis in our study. This is contrary to a study [5] of 293 patients with NSCLC at a IIIB-IV clinical stage that showed that in patients with an adenocarcinoma histological type, CEA levels greater than 40 ng/mL predicted CNS metastasis. Therefore, more studies are required

to further investigate the relationship between serum CEA and metastasis.

Our study did not find serum CEA to be a prognostic factor for 2-year mortality. The use of the pretreatment CEA level as a prognostic marker for NSCLC has been extensively investigated, but the results have been conflicting [12-20]. In a study [21] involving 105 patients with all stages of NSCLC, CEA was found to be a significant negative prognostic factor. However, in another study [22] on 200 patients with stage I-IV disease, CEA was not found to be a prognostic factor for survival. Due to these conflicting results, and even though CEA was recommended for prognostic use in the National Academy of Clinical Biochemistry Guidelines [23], the American Cancer Society (ACS) and the American Society of Clinical Oncology (ASCO) have not as yet published recommendations for its prognostic use. Nevertheless, CEA should be considered when predicting risk of relapse, progression and the effect of treatment.

There were some limitations to our study that should be mentioned. The retrospective design of the study brought with it several disadvantages, including non-uniform serum CEA collection time-points prior to chemotherapy, and the inability to control confounding factors such as chemotherapy duration or any additional therapy such as radiotherapy. Nevertheless, there were also strengths in this study. First, we were able to recruit patients at various stages of NSCLC, which allowed us to examine the correlation of CEA in different stage spectrums of NSCLC. Also, the cut-off serum CEA level was selected in a way that normal variants (for example, a high CEA level in a smoker) had minimal impact on the interpretation of our results.

Conclusion

Our study found that in patients with NSCLC, high CEA levels were associated with adenocarcinoma cell type, more advanced stage, and higher risks of metastasis. Age ≥70 years, advanced disease stage, and poor PS were prognostic factors for 2-year mortality. Serum CEA level was not a prognostic factor for mortality in patients with NSCLC in our study.

Acknowledgment

The authors would like to thank all of the staff and clinicians in the Division of Pulmonary and Critical Care Medicine of Kaohsiung Chang Gung Memorial Hospital who participated in this study for their support.

References

1. Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
2. Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer (Amsterdam, Netherlands) 2012; 76: 138-43.
3. Gibbs AR, Thunnissen FB. Histological typing of lung and pleural tumours: third edition. J Clin Pathol 2011; 54: 498-9.
4. Edge S, Compton C. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. Ann Surg Oncol 2010; 17: 1471-4.
5. Arrieta O, Saavedra-Perez D, Kuri R, *et al*. Brain metastasis development and poor survival associated with carcinoembryonic antigen (CEA) level in advanced non-small cell lung cancer: a prospective analysis. BMC Cancer 2009; 9: 119.
6. Quayle JB. Ability of CEA blood levels to reflect tumour burden: a study in a human xenograft model. Brit J of Cancer 1982; 46: 220-7.
7. Muley T, Fetz TH, Dienemann H, *et al*. Tumor volume

and tumor marker index based on CYFRA 21-1 and CEA are strong prognostic factors in operated early stage NSCLC. Lung Cancer (Amsterdam, Netherlands) 2008; 60: 408-15.

8. Shinkai T, Saijo N, Tominaga K, *et al*. The value of carcinoembryonic antigens in patients with advanced lung cancer: in relation to chemotherapy. Gan to kagaku ryoho. Cancer & Chemotherapy 1984; 11: 1056-63.
9. Jessup JM, Petrick AT, Toth CA, *et al*. Carcinoembryonic antigen: enhancement of liver colonisation through retention of human colorectal carcinoma cells. B J Cancer 1993; 67: 464-70.
10. Thomas P, Forse RA, Bajenova O. Carcinoembryonic antigen (CEA) and its receptor hnRNP M are mediators of metastasis and the inflammatory response in the liver. Clin Exper Metas 2011; 28: 923-32.
11. Hostetter RB, Augustus LB, Mankarious R, *et al*. Carcinoembryonic antigen as a selective enhancer of colorectal cancer metastasis. J Natl Cancer Inst 1990; 82: 380-5.
12. Barlesi F, Gimenez C, Torre JP, *et al*. Prognostic value of combination of Cyfra 21-1, CEA and NSE in patients with advanced non-small cell lung cancer. Respir Med 2004; 98: 357-62.
13. Barak V, Goike H, Panaretakis KW, *et al*. Clinical utility of cytokeratins as tumor markers. Clin Biochem 2004; 37: 529-40.
14. Diez M, Torres A, Maestro ML, *et al*. Prediction of survival and recurrence by serum and cytosolic levels of CEA, CA125 and SCC antigens in resectable non-small-cell lung cancer. Brit J Cancer 1996; 73: 1248-54.
15. Pollan M, Varela G, Torres A, *et al*. Clinical value of p53, c-erbB-2, CEA and CA125 regarding relapse, metastasis and death in resectable non-small cell lung cancer. Internatl J Cancer. (Journal International du Cancer) 2003; 107: 781-90.
16. Muley T, Dienemann H, and Ebert W. Increased CYFRA 21-1 and CEA levels are negative predictors of outcome in p-stage I NSCLC. Anticancer Res 2003; 23: 4085-93.
17. Muley T, Dienemann H, and Ebert W. CYFRA 21-1 and CEA are independent prognostic factors in 153 operated stage I NSCLC patients. Anticancer Res 2004; 24: 1953-6.
18. Okada M, Nishio W, Sakamoto T, *et al*. Prognostic significance of perioperative serum carcinoembryonic antigen in non-small cell lung cancer: analysis of 1,000 consecutive resections for clinical stage I disease. Annals Thorac Surg 2004; 78: 216-21.
19. Hanagiri T, Sugaya M, Takenaka M, *et al*. Preoperative CYFRA 21-1 and CEA as prognostic factors in patients with stage I non-small cell lung cancer. Lung Cancer (Amsterdam, Netherlands) 2011; 74: 112-7.
20. Schneider J, Philipp M, Velcovsky HG, *et al*. Pro-gastrin-releasing peptide (ProGRP), neuron specific enolase (NSE), carcinoembryonic antigen (CEA) and cytokeratin 19-fragments (CYFRA 21-1) in patients with lung cancer in comparison to other lung diseases. Anticancer Res 2003; 23: 885-93.
21. Moro D, Villemain D, Vuillez JP, *et al*. CEA, CYFRA21-1 and SCC in non-small cell lung cancer. Lung Cancer (Amsterdam, Netherlands) 1995; 13: 169-76.
22. Kulpa J, Wojcik E, Reinfuss M, *et al*. Carcinoembryonic antigen, squamous cell carcinoma antigen, CYFRA 21-1, and neuron-specific enolase in squamous cell lung cancer patients. Clin Chem 2002; 48: 1931-7.
23. Stieber P, Hatz R, Holdenrieder S, *et al*. National Academy of Clinical Biochemistry: Practice Guidelines And Recommendations For Use Of Tumor Markers In Clinical Lung Cancer (Section 3P)

血清癌胚抗原在未接受化學治療的非小細胞肺癌患者之預測價值

高旭卿 * 張晃智 * 林孟志 *,** 方文豐 *,** 黃國棟 * 曾嘉成 *
劉世豐 *,** 王金洲 *,**

背景：癌胚抗原（CEA）是一個已知的非小細胞肺癌（NSCLC）的標記。而在一些針對非小細胞肺癌患者中的小樣本研究中發現，癌胚抗原是這些患者死亡率和預後不良的一個危險因素。本研究目的是評估血清癌胚抗原值，在不同腫瘤分期且未接受化學治療，且較大樣本數的非小細胞肺癌患者中之預測價值。

方法：251 位患有第 2 期至第 4 期非小細胞肺癌者，其血清癌胚抗原值在接受化療前接受測量。之後 251 位患者於 2008/01 to 2011/12 期間，在高雄長庚紀念醫院接受 cisplatin and gemcitabine 的第一線化學治療。這些病人被分為兩組：一組其血清癌胚抗原值在接受化療前大於等於 40 ng/mL，另一組血清癌胚抗原值小於 40 ng/mL。我們分析此兩組病人在臨床特徵，總生存率，以及 2 年死亡率之差異。另外，我們也檢視血清癌胚抗原值與癌症轉移部位之關聯性。

結果：在 251 個患者中，183 位（72.9%）其血清癌胚抗原值小於 40 ng/mL，68 位（27.1%）血清癌胚抗原值大於等於 40 ng/mL。單變項分析發現肺腺癌（p=0.014），後期肺癌（p=0.007），以及癌細胞轉移（p=0.037）與血清癌胚抗原值大於或於 40 ng/mL 有關。Cox 多變項回歸分析結果顯示病人體能狀態，癌症分期，以及患者年齡大於等於 70 歲為非小細胞肺癌患者死亡的獨立預測因子。血清癌胚抗原值並非患者死亡與否的預測因子，也無法預測 IIIb 期患者之後癌症轉移部位。

結論：在此研究中，血清癌胚抗原不是非小細胞肺癌患者死亡的預測因子。*(胸腔醫學* ***2014; 29: 200-208)***

關鍵詞：非小細胞肺癌，血清癌胚抗原，死亡，預測因子

* 長庚大學醫學院　高雄長庚紀念醫院　內科部　胸腔內科
** 長庚大學醫學院　高雄長庚紀念醫院　呼吸治療學系
索取抽印本請聯絡：王金洲醫師，高雄長庚紀念醫院　內科部　胸腔內科，高雄市鳥松區大埤路 123 號

High Incidence of Treatment-Related Hypothyroidism in Multidrug-Resistant Tuberculosis Patients

Wan-Chun Huang, Cheng-Wei Huang, Ko-Ming Hsu,
Shen-Hsuan Chien, Ming-Chih Yu

Background: Hypothyroidism is a known adverse effect of treatment for multidrug-resistant tuberculosis (MDR-TB). It has been suspected to be rare; however, recent studies report an incidence ranging from 3.5% to 71.4%. Development of hypothyroidism is considered to be attributed to the administration of prothionamide, ethionamide, and p-aminosalicylic acid, but whether a combination of these drugs influences this development is not known. The present study retrospectively analyzed the incidence of hypothyroidism in patients treated for MDR-TB and the correlation with these drugs.

Methods: The records of 50 patients treated for MDR-TB from January 1, 2009 to March 31, 2012 were retrospectively analyzed. All patients were followed until completion of treatment, or until March 31, 2012. Data regarding patient characteristics, co-morbidities, baseline blood test and thyroid function test results, administration of prothionamide and p-aminosalicylic acid, and thyroid-stimulation hormone (TSH) levels during treatment were extracted for analysis.

Results: Twenty-four (48%) of the 50 patients developed hypothyroidism. The median and mean times from start of treatment to detection of hypothyroidism were 151 days and 162 days, respectively. Patients who developed hypothyroidism were significantly younger (p=0.045) than those who did not. Prothionamide and p-aminosalicylic acid were found to be associated with hypothyroidism development. The combination of these 2 drugs was associated with a higher risk of developing hypothyroidism (odds ratio=4.385, p=0.03) than the use of prothionamide alone.

Conclusion: Hypothyroidism is relatively common in patients treated for MDR-TB. The incidence is higher in patients receiving a combination of prothionamide and p-aminosalicylic acid. Clinicians should be aware of this possible adverse effect, and watch for clinical symptoms and signs suggesting hypothyroidism, especially in young patients and during the first few months of treatment. Beginning TSH testing as early as 1 month after beginning treatment may be appropriate. ***(Thorac Med 2014; 29: 209-217)***

Key words: multidrug-resistant tuberculosis, hypothyroidism, prothionamide, p-aminosalicylic acid

Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University
Address reprint requests to: Dr. Ming-Chih Yu, Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, No. 111, Section 3, Hsin-Long Road, Taipei, Taiwan

Introduction

The World Health Organization (WHO) recently reported a reduced number of tuberculosis (TB) patients globally. However, 3.7% of new cases and 20% of previously treated cases worldwide are estimated to have multidrug-resistant TB (MDR-TB), which is defined as TB that is resistant to at least isoniazid and rifampicin [1]. According to the WHO guidelines, at least 4 effective drugs, including an injectable drug, are suggested as combination chemotherapy to avoid treatment failure and drug resistance in cases of MDR-TB [2].

Nevertheless, poor adherence to treatment due to the side effects of medications remains a major concern in treating patients with MDR-TB. Known side effects include skin rash, gastrointestinal upset, nephrotoxicity, hepatotoxicity and psychosis. Since poor drug adherence probably leads to more drug resistance, managing side effects is indeed crucial [3].

Hypothyroidism is a known side effect related to the treatment of MDR-TB, and has been suspected to be rare. However, studies in the past decade have reported an incidence ranging from 3.5 to 71.4% [4-9]. The reason for this wide variation is not known, and there is no published data regarding the incidence of hypothyroidism among Taiwan's MDR-TB patient population.

The development of hypothyroidism in MDR-TB patients is considered to be related to the administration of certain medications, especially prothionamide, ethionamide, and p-aminosalicylic acid. However, whether the combination of these drugs influences hypothyroidism development is not known.

The purpose of this retrospective study was to determine the incidence of hypothyroidism among patients receiving treatment for MDR-TB in Taiwan. Patient characteristics and drugs related to the development of hypothyroidism were also evaluated.

Methods

Study setting

This retrospective study included all patients who received treatment for MDR-TB at Taipei Medical University-Wan Fang Hospital from January 1, 2009 to March 31, 2012. Patients who did not participate in the "directly observed treatment, short-course-plus" (DOTS-Plus) program were excluded. In addition, patients who had hypothyroidism before MDR-TB treatment and who did not have subsequent thyroid-stimulating hormone (TSH) levels examined during post-treatment follow-up were also excluded.

The treatment regimens for MDR-TB were designed by chest specialists according to the WHO guideline [2]. The initial regimens consisted of effective first-line drugs, an injectable drug, a fluoroquinolone, and other second-line oral drugs to ensure there were at least 4 effective anti-TB drugs. Subsequent drug regimens were adjusted based on drug susceptibility test results and side effects.

All patients underwent testing of their baseline thyroid function before treatment. Subsequent thyroid function measurements were done based on clinical symptoms and physician judgment. Patient characteristics, co-morbidities, previous first-line and second-line drug treatment history, and other baseline biochemistry and hemogram data were collected for risk factor stratification. Data regarding exposure to and dosage of prothionamide and p-aminosalicylic acid were also extracted to identify their correlation with the development of hypothy-

roidism. Patients were followed until completion of treatment or until March 31, 2013, the study end date.

Hypothyroidism was defined according to clinical practice guidelines from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The National Health and Nutrition Examination Survey (NHANES III) [10-11]. Hypothyroidism was defined as (1) a free-T4 level <0.93 ng/dl with a TSH level >4.5 mIU/l, or (2) a free-T4 level between 0.93-1.71 ng/dl with a TSH level >10.0 mIU/l.

Statistical analysis

Continuous variables were compared using the *t*-test, and categorical variables were analyzed with the Chi-square test. Correlation between the development of hypothyroidism and usage of prothionamide and p-aminosalicylic acid were examined with logistic regression analysis. The Kaplan-Meier method was used for analysis of hypothyroidism occurrence during the period of MDR-TB treatment. *p* values <0.05 were considered statistically significant. Statistical analyses were conducted with SPSS version 17 software (IBM).

Results

From January 1, 2009 to March 31, 2012, 54 patients received MDR-TB treatment in the DOTS-Plus program at Taipei Medical University-Wan Fang Hospital. One patient with hypothyroidism before the start of MDR-TB treatment was excluded, and 3 patients without TSH levels during follow-up after treatment were also excluded. Thus, 50 patients, their clinical characteristics, co-morbidities, blood test results, and baseline TSH and free-T4 levels (Table 1), were included for analysis. The patients who developed hypothyroidism were significantly younger those that did not.

The mean baseline TSH level was 1.71 mIU/l. The mean number of TSH results per patient was 5.3; the number for patients who developed hypothyroidism was higher than for those that did not (6.6 vs. 4.0).

During the treatment period, 24 patients (48%) developed hypothyroidism. The median and mean times from start of MDR-TB treatment to detection of the development of hypothyroidism were 151 days and 162 days, respectively, with a range of 29-460 days (Figure 1).

Of the 24 patients who developed hypothyroidism, 23 (95.8%) received prothionamide and 20 (83.3%) also received p-aminosalicylic acid (Figure 2). One patient received a regimen without prothionamide and p-aminosalicylic acid, and another received p-aminosalicylic acid but not prothionamide. These 2 patients were not separately analyzed because of the small case numbers. Patients who received prothionamide plus p-aminosalicylic acid had more than 4 times the risk of developing hypothyroidism than patients that received prothionamide alone (Table 2).

Among these 24 patients, 9 (37.5%) had clinical symptoms or signs of hypothyroidism. All of them complained of general weakness or lethargy. Two had poor appetite and 1 had cold intolerance. An enlarged thyroid gland was noticed in 1 patient. We discontinued the suspected offending agent (prothionamide or p-aminosalicylic acid) for 4 of the 9 patients, provided a thyroid hormone supplement for 3 patients, and a thyroid hormone supplement along with discontinuation of the offending agent for the remaining 2 patients. They all returned to an euthyroid status after the above management.

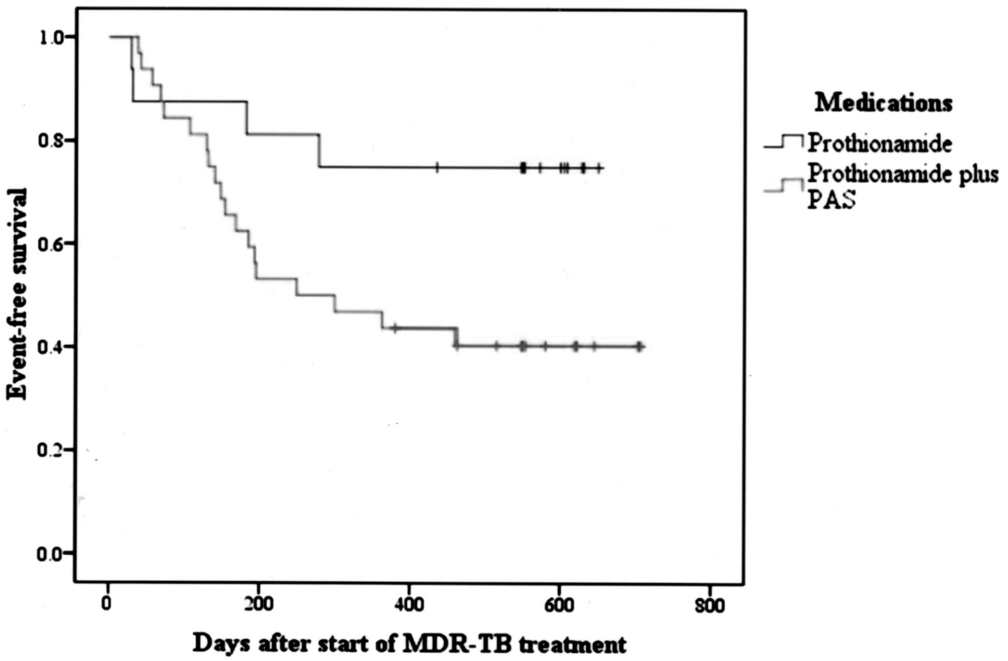
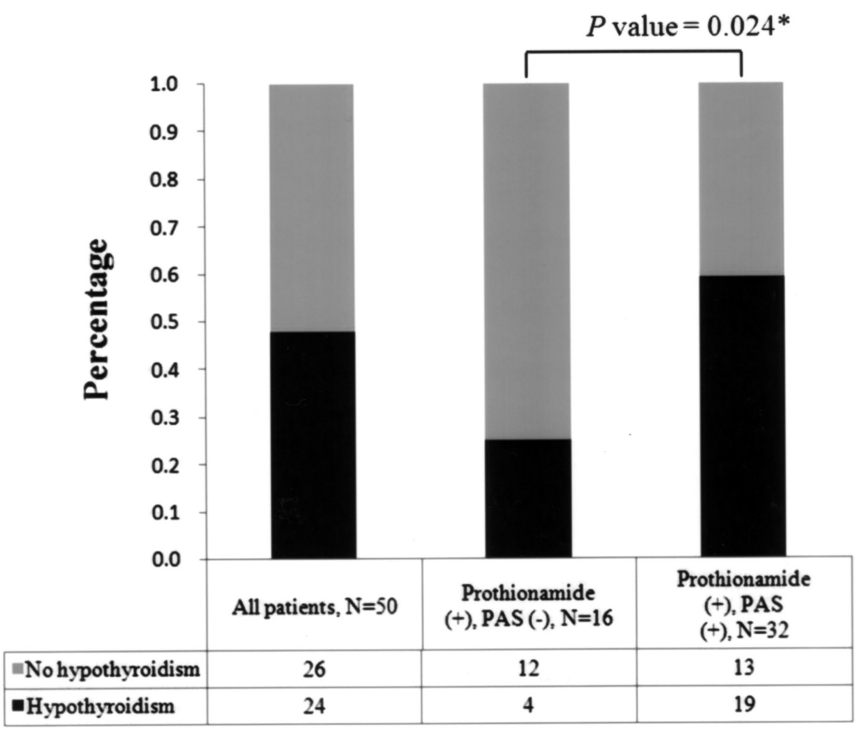


Fig. 1. Kaplan-Meier estimate of the proportion of patients developing hypothyroidism after treatment for multidrug-resistant tuberculosis. MDR-TB, multidrug-resistant tuberculosis; PAS, p-aminosalicylic acid.



	All patients, N=50	Prothionamide (+), PAS (-), N=16	Prothionamide (+), PAS (+), N=32
No hypothyroidism	26	12	13
Hypothyroidism	24	4	19

Fig. 2. Bar chart showing the incidence of hypothyroidism development in patients treated for multidrug-resistant tuberculosis. Patients treated with prothionamide plus p-aminosalicylic acid (PAS) had a higher rate of hypothyroidism development.

Table 1. Clinical Characteristics of the Multidrug-Resistant Tuberculosis Patients

Characteristics	Patients without hypothyroidism (n=26)	Patients with hypothyroidism (n=24)	*p* value
Age (year)	53.5±18.3	42.7±18.8	0.045*
Male gender	17 (65.4)	16 (66.7)	1.000
Body mass index (kg/m^2)	20.7±3.6	20.8±5.0	0.912
Smoking habit	15 (57.7)	11 (45.8)	0.579
Family history of tuberculosis	5 (19.2)	6 (25.0)	0.881
History of previous drug use			
New case	17 (65.4)	15 (62.5)	1.000
Previous treatment with 1st-line drugs	8 (30.8)	8 (33.3)	1.000
Previous treatment with 2nd-line drugs	1 (3.8)	1 (4.2)	1.000
Comorbidity			
Diabetes mellitus	7 (26.9)	6 (25.0)	1.000
Hypertension	7 (26.9)	5 (20.8)	0.863
Hepatitis B	1 (3.8)	5 (20.8)	0.158
Hepatitis C	1 (3.8)	4 (16.7)	0.299
Baseline blood tests			
Hemoglobin (g/dl)	12.5±2.1	12.5±1.5	0.979
AST (U/l)	29±17	24±7	0.169
ALT (U/l)	28±32	17±7	0.111
Creatinine (mg/dl)	1.26±1.89	1.12±1.74	0.801
TSH (mIU/l)	1.91±1.33	1.53±1.09	0.287
Free-T4 (ng/dl)	1.04±0.11	1.09±0.15	0.228
Drug dosage			
Prothionamide (mg/kg)	10.3±1.8	10.5±2.4	0.666
P-aminosalicylic acid (mg/kg)	152.5±26.2	161.3±47.3	0.503

Abbreviations: TSH, thyroid stimulating hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Data are presented as mean±SD or No. (%).

*p value <0.05

Table 2. Logistic Regression Analysis of the Occurrence of Hypothyroidism

Variables	Odds Ratio	95% Confidence Interval	*p* value
Prothionamide	Reference	-	-
Prothionamide plus p-aminosalicylic acid	4.385	1.156-16.636	0.030*

*p value <0.05

Discussion

MDR-TB is an emerging global public health threat. The overall treatment success of MDR-TB is only 48%, and 28% of cases are reported as lost to follow-up or have no outcome information [1]. These data indicate the necessity of a better patient management and follow-up program. Drug side effects and related poor adherence to treatment, which could lead to more drug resistance, are still major problems; therefore, monitoring and managing of drug side effects cannot be overlooked.

The incidence of the development of hypothyroidism in patients treated for MDR-TB is higher than previously expected. Nathanson *et al*. [5] reported an incidence of 3.5% in a total of 818 MDR-TB patients. Satti *et al*. [6-7], following the WHO guideline recommendations for routine testing of TSH at 6 and 12 months, reported that of 186 patients tested, 129 (69%) had hypothyroidism. Gupta *et al*. [8] also demonstrated that 71.4% of patients receiving treatment for MDR-TB developed hypothyroidism. In our study, 48% of patients developed hypothyroidism during treatment for MDR-TB. Our result confirmed that hypothyroidism is relatively common in patients receiving MDR-TB treatment.

Possible risk factors related to the development of hypothyroidism are of clinical importance. Among the aforementioned studies, only 1 found that male sex was associated with the development of hypothyroidism [9]. No risk factors were reported in any of the other studies. In our study population, we found that patients who developed hypothyroidism were younger than those who did not, and the difference was statistically significant. This finding indicates the need for awareness of the possible development of hypothyroidism in young MDR-TB patients.

The development of hypothyroidism in patients treated for MDR-TB was suspected to be related to the administration of prothionamide, ethionamide, and p-aminosalicylic acid. Prothionamide and ethionamide are thionamide derivatives of isonicotinic acid, and their structures are similar to other thionamides, such as methimazole and propylthiouracil. It is believed that they can inhibit the synthesis of thyroid hormone through inhibition of iodine organification. P-aminosalicylic acid is one of the oldest anti-TB medications, and is also believed to cause hypothyroidism through inhibition of iodine organification. However, whether a combination of these drugs influences hypothyroidism development has not been documented.

Our result confirmed the contribution of prothionamide and p-aminosalicylic acid to hypothyroidism development in patients treated for MDR-TB. We found that 25% and 59% of patients who received prothionamide alone and prothionamide plus p-aminosalicylic acid, respectively, developed hypothyroidism, and the risk of hypothyroidism in the later patient group was significantly higher (odds ratio: 4.385, p=0.03).

WHO guidelines published in 2011 indicate that regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid if cycloserine cannot be used. Cycloserine may cause psychotic symptoms and depression, which limit its use. However, because of the high incidence of hypothyroidism in patients receiving the combination of prothionamide and p-aminosalicylic acid, the choice between these second-line oral medications should be prudently considered to

avoid poor patient compliance.

The WHO guidelines recommend that patients should be screened for hypothyroidism with a serum TSH test at 6 months after beginning treatment. However, the median time to hypothyroidism development in our patients was 151 days, indicating more than half of our patients had developed hypothyroidism by 6 months. In addition, the shortest time to the development of hypothyroidism was 29 days after the start of treatment. Thus, to avoid the consequences of a delayed diagnosis, screening of TSH levels at 1, 3, and 6 months after the start of treatment may be appropriate. Of note, most of our patients had subtle symptoms, further suggesting that routine measurement may avoid a delay in diagnosis. Subsequent measurement should be done based on clinical suspicion.

After detection of hypothyroidism, WHO guidelines suggest thyroid hormone supplement since drug choices are limited in patients with MDR-TB [7]. Rather than thyroid hormone supplement, Dutta et al. reported a case series of patients with improved thyroid function after discontinuation of ethionamide alone [12]. All our patients with symptomatic hypothyroidism returned to an euthyroid status after thyroid hormone supplement, discontinuation of the offending drugs, or both. Clinicians should take the patient's drug adherence and available drug choices into consideration for management after hypothyroidism is detected.

There are limitations to this study. This was a retrospective study, and TSH levels were not measured on a regular basis, which might have delayed the diagnosis and decreased the detection rate. Most of our patients received prothionamide in accordance with WHO guidelines. Instead of p-aminosalicylic acid, some patients were given cycloserine or other drugs. As a result, only 1 patient received a regimen containing p-aminosalicylic acid but no prothionamide. The contribution of p-aminosalicylic acid alone to the development of hypothyroidism could not be evaluated. Nevertheless, the results suggest that p-aminosalicylic acid is associated with a higher risk of hypothyroidism development.

In conclusion, our study found that hypothyroidism is relatively common in patients treated for MDR-TB. The incidence was higher in patients receiving a combination of prothionamide and p-aminosalicylic acid. Clinicians should be aware of this possible adverse effect, and watch for clinical symptoms and signs suggesting hypothyroidism, especially in young patients and during the first few months of treatment. We suggest examining TSH levels beginning 1 month after starting treatment, and then checking them on a regular basis. However, further prospective studies are needed for a more appropriate screening and monitoring protocol.

Acknowledgements

This study was supported by the MDR-TB program of the Centers for Disease Control, Department of Health, Taiwan.

References

1. World Health Organization. Global tuberculosis report. ISBN 978 92 4 156450 2. Geneva; WHO, 2012. Available at: http://www.who.int/tb/publications/global_report/gtbr12_main.pdf.
2. Falzon D, Jaramillo E, Schünemann HJ, *et al*. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J 2011; 38: 516-28.
3. Pritchard AJ, Hayward AC, Monk PN, *et al*. Risk factors for drug resistant tuberculosis in Leicestershire – poor

adherence to treatment remains an important cause of resistance. Epidemiol Infect 2003; 130: 481-3.
4. Furin JJ, Mitnick CD, Shin SS, *et al*. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2001; 5: 648-55.
5. Nathanson E, Gupta R, Huamani P, *et al*. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis 2004; 8: 1382-4.
6. Satti H, Mafukidze A, Jooste P L, *et al*. High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. Int J Tuberc Lung Dis 2012; 16: 468-72.
7. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402. Geneva, Switzerland: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf
8. Gupta J, Breen RAM, Milburn HJ, *et al*. Drug-induced hypothyroidism in patients receiving treatment for multidrug-resistant tuberculosis in the UK. Int J Tuberc Lung Dis 2012; 16: 1278.
9. Modongo C, Zetola NM. Prevalence of hypothyroidism among MDR-TB patients in Botswana. Int J Tuberc Lung Dis 2012; 16: 1561-2.
10. Garber JR, Cobin RH, Gharid Hossein, *et al*. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012; 22: 1200-35.
11. Hollowell JG, Staehling NW, Flanders WD, *et al*. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489-99.
12. Dutta BS, Hassan G, Waseem Q, *et al*. Ethionamide-induced hypothyroidism. Int J Tuberc Lung Dis 2012; 16: 141.

多重抗藥性結核治療產生高發生率的甲狀腺功能低下症

黃萬均　黃晟維　徐克明　簡慎萱　余明治

背景：甲狀腺功能低下症是已知的多重抗藥性結核治療副作用，在過去被認為是罕見的狀況，然而最近文獻報導的發生率介於 3.5 到 71.4%。甲狀腺功能低下症的發生被認為和丙硫異煙胺、乙硫磷醯胺及對氨基水楊酸有關，但合併這些藥物的使用是否影響甲狀腺功能低下症的發生並不清楚。本研究回顧性分析多重抗藥性結核病人產生甲狀腺功能低下症的機率以及與這些藥物的相關性。

方法：本研究回顧性分析從 2009 年 1 月 1 日至 2012 年 3 月 31 日開始接受治療的 50 位多重抗藥性結核病人，並且這些病人都追蹤至治療完成或至少到 2013 年 3 月 31 日。我們收集病人的臨床特徵、共病、基礎血液檢測及甲狀腺功能、丙硫異煙胺和對氨基水楊酸的使用以及促甲狀腺激素數值進行分析。

結果：50 位病人中有 24 位（48%）發生甲狀腺功能低下症，從治療開始到檢測出甲狀腺功能低下症的中位時間及平均時間分別為 151 天及 162 天，發生甲狀腺功能低下症的病人比起沒有發生的病人明顯較年輕（p=0.045）。丙硫異煙胺及對氨基水楊酸和甲狀腺功能低下症的發生有關聯性，這兩種藥物合併使用比單純使用丙硫異煙胺有更高的發生率（odds ratio=4.385, p=0.03）。

結論：甲狀腺功能低下症在接受多重抗藥性結核治療的病人中是常見的，在合併使用丙硫異煙胺和對氨基水楊酸的病人中其發生率更高。臨床人員應該留意這個可能的副作用，並且觀察相關的臨床症狀，特別是較年輕的病人及開始治療的前幾個月。我們認為，開始治療後一個月即進行促甲狀腺素的測量可能是必要的。*(胸腔醫學* ***2014; 29: 209-217)***

關鍵詞：多重抗藥性結核，甲狀腺功能低下症，丙硫異煙胺，對氨基水楊酸

臺北醫學大學　市立萬芳醫院內科部　胸腔內科
索取抽印本請聯絡：余明治醫師，臺北醫學大學　市立萬芳醫院　胸腔內科，臺北市文山區興隆路三段 111 號

Primary Tracheal Squamous Cell Carcinoma - Presenting with Circumferential Invasion and Treated with Photodynamic Therapy

Lih-Yu Chang*, Sheng-Kai Liang**, Chia-Lin Hsu*, Jang-Ming Lee***, Chong-Jen Yu*

Primary neoplasms of the trachea are extremely rare. The diagnosis usually depends on computed tomography (CT) scan. We report a 50-year-old woman who suffered from chronic productive cough for 1 year. Roentgenograms and chest CT showed no abnormal finding. Bronchoscopy showed diffuse circumferential papilloma-like lesions at the trachea. Endobronchial ultrasound showed submucosal invasion of the trachea. The pathology of the endotracheal biopsy showed squamous cell carcinoma. She received photodynamic therapy as first-line treatment with a good response and tumor regression. ***(Thorac Med 2014; 29: 218-223)***

Key words: squamous cell carcinoma, tracheal tumor, bronchoscopy, endobronchial ultrasound, photodynamic therapy

Introduction

Primary tracheal tumors are rare, and are usually malignant in adults (80-90%) and benign in children (60-70%) [1-2]. Clinical presentations include dyspnea (58%), cough (54%), hemoptysis (45%), wheezing (36%) and stridor (24%) [3]. Diagnosis is often delayed for months due to initial misdiagnosis as asthma, chronic obstructive airway disease, or chronic bronchitis.

The conventional chest radiograph is usually not diagnostic. Computed tomography (CT) scan is the most important imaging tool for diagnosis of tracheal tumor and evaluation of the relationship between the surrounding tissue and organs [1]. Pulmonary function test may show fixed upper airway obstruction [1]. Bronchoscopy is used for tissue sampling and assessment of the location and extent of the disease [1].

In previous reports, tracheal tumor almost always presented with a protruding mass and could be easy diagnosed by chest CT. We present a case of primary tracheal squamous cell carcinoma with circumferential invasion, which is difficult to diagnose with chest CT. The patient was treated with photodynamic therapy (PDT) after diagnosis.

*Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan
**Department of Internal Medicine, National Taiwan University Hospital, Hsinchu branch, Hsinchu, Taiwan
***Department of Surgery, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan
Address reprint requests to: Dr. Chia-Lin Hsu, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, No. 7, Chung Shan S. Rd., Zhongzheng Dist., Taipei City, Taiwan (R.O.C.)

Case Report

A 50-year-old woman with a history of hyperthyroidism under medical control suffered from chronic productive cough for 1 year. Her symptom exacerbated when in contact with cold air or cold water. No fever, chills, dyspnea, or body weight loss was noted during this period. She first visited a hospital in Hsinchu City, where the chest radiography (Figure 1) and pulmonary function test each showed no abnormal findings. Chest CT revealed no lung parenchymal lesion or endotracheal/endobronchial lesion. She was transferred to our hospital for further work-up. Bronchoscopy was performed and showed diffuse tracheal mucosal swelling with circumferential papilloma-like lesions (Figure 2). The tracheal tumor was located from 2 cm below the vocal cord to 1 cm above the carina, with a total length of about 6.5 cm. Endobronchial ultrasound (EBUS) with radial probe was performed to evaluate the depth of tracheal invasion, and showed the tumor submucosal invasion. Malignant neoplasm was suspected and several endobronchial biopsies were taken from the papilloma-like lesion. Pathology showed squamous cell carcinoma and dysplastic squamous epithelium. The squamous cell carcinoma showed diffuse and strong positive immunoreactivity to p16. Since the human papilloma virus (HPV) can degrade retinoblastoma protein and lead to aberrant overexpression of p16, the pathology presentation was compatible with HPV-related neoplasm [4]. No evidence of gastrointestinal tract malignancy or nasopharyngeal cancer was seen. The final diagnosis was primary tracheal squamous cell carcinoma. Staging work-up for primary tracheal cancer was then completed. The final stage was $T_4N_0M_0$, stage IIIA, according to the 7th edition of the TNM system for lung and pleural tumors, but the stage was changed to $T_2N_0M_0$, stage II, using the staging system proposed by Bhattacharyya [5].

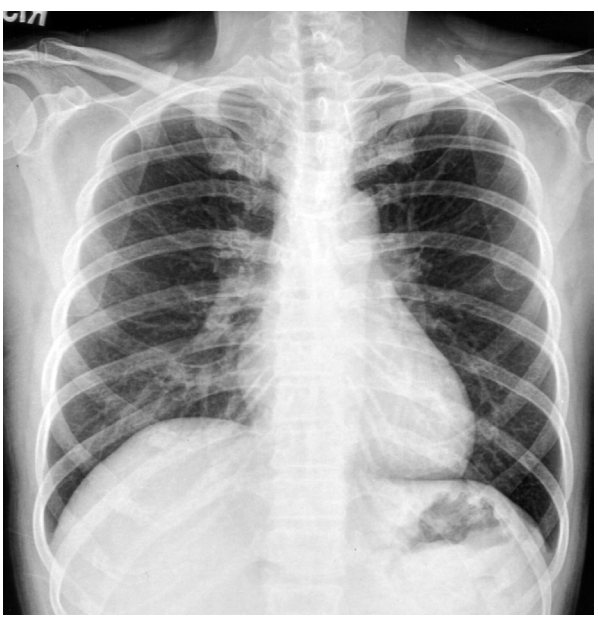


Fig. 1. No definite airway or parenchymal lesion was noted in the chest X-ray.

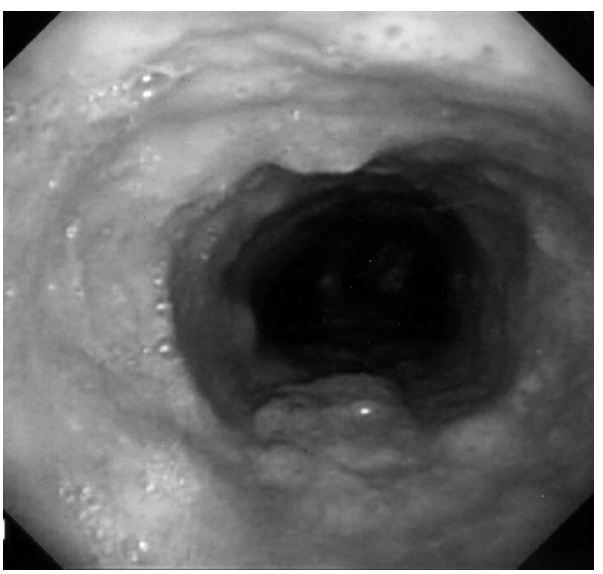


Fig. 2. Bronchoscopy showed diffuse papilloma-like lesions with circumferential involvement of the trachea (before photodynamic therapy)

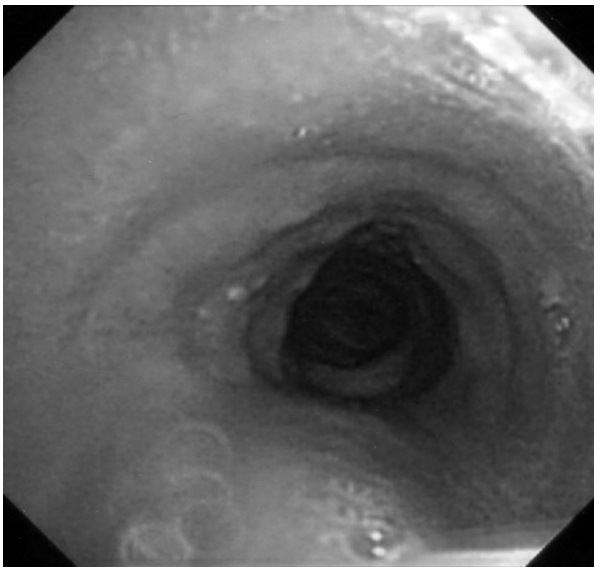


Fig. 3. Tracheal tumor regression was noted with bronchoscopy after photodynamic therapy

After discussion with the patient and her family, she underwent PDT (energy: 200J, 2 times, with cytotoxic photosensitizer porfimer sodium (PHOTOFRIN®) 2 mg/kg body weight). Tumor necrosis with debris-induced airway obstruction occurred repeatedly after PDT (Figure 3). At least 3 episodes of acute airway obstruction occurred within 3 days after PDT. The airway obstruction was relieved by bronchoscopic intervention with removal of the tumor debris. After rigid bronchoscopy with tracheal debridement, the patient was able to wean off the ventilator and extubated successfully. The follow-up endotracheal biopsies 1, 3, and 5 months after PDT showed no evidence of residual malignant cells. However, she suffered from tracheal stenosis with the clinical presentation of progressive dyspnea about 45 days after PDT. Balloon dilatations were performed several times, but tracheal re-stenosis occurred repeatedly and endotracheal stent implantation had to be performed about 3 months after PDT.

Discussion

Primary tracheal neoplasm is a rare type of malignancy (0.2% of all respiratory tract malignancies; 0.04% of all malignancies) [6]. Squamous cell carcinoma and adenoid cystic carcinoma are the most common types and comprise about two-thirds of all adult primary tracheal tumors. Other pathologic types including adenocarcinoma, large-cell undifferentiated carcinoma, neuroendocrine tumors, and soft-tissue-type sarcoma [1-2]. Chest radiography usually shows no abnormality and the diagnosis is usually dependent on chest CT scan. However, the CT scan could not demonstrate the endotracheal lesion in our patient due to circumferential tumor invasion without a mass protruding into the tracheal lumen.

The diagnosis of our patient was dependent on bronchoscopy, for the following reasons. First, the tracheal cancer could be seen by bronchoscopy due to the character of the lesion morphology alone. Second, endobronchial biopsy disclosed the nature of the tracheal cancer. Third, the EBUS result showed a lesion with submucosal invasion. The trachea and bronchus laminar histologic structure could be identified by EBUS, as well [7]. With the EBUS result, we could determine whether the tracheal lesion was within the tracheal wall or had invaded other neighborhood structures.

The American Joint Committee for Cancer (AJCC) and Union for International Cancer Control (UICC) have not established a staging-ing system for primary tracheal cancer. Only 2 staging systems were proposed in 2004 and 2006 [1,5]. Due to the rarity of cases, the value and outcome of the predictive effect of the 2 staging systems requires further investigation.

The current recommendation for treatment

of tracheal malignancy is surgery [6]. The alternative choices of treatment include radiotherapy, systemic chemotherapy treatment and endotracheal treatment [8]. Of the alternative treatment modalities, endotracheal treatment could relieve the airway obstruction caused by the tumor mass sooner. The endotracheal treatment techniques include mechanical core-out, electrocoagulation, neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, carbon dioxide laser or argon beam coagulation, and cryotherapy or PDT.

PDT, which was developed in the 1970s, can target cancer selectively by exposing the target site to light after administration of a photosensitizer [9-10]. In general, the indications for PDT include palliative treatment of tracheobronchial tree advanced obstructing cancers, and curative treatment of asymptomatic early lung cancer [11-14]. Due to the delayed effect and possible swelling following therapy, trachea-carina lesions have been considered as a relative contraindication for PDT [15]. Few studies have discussed the use of PDT in tracheal malignancy treatment [9,11,16-18], and only 1 study focused on primary tracheal cancer [9]. Martin LK, *et al*. reported a case series with 10 primary tracheal carcinoma patients who received PDT. Eight patients showed an objective response with observed tumor regression within 1 month after PDT, and 5 of 7 patients who received post-treatment biopsies had negative biopsies of the tumor site within 1 month of treatment. Most patients had no acute PDT-related complication within the first 30 days after treatment, only 1 patient suffered from tracheal stenosis 2 months after the third PDT and needed balloon dilatation and endotracheal stent management.

The other studies discussing PDT use for airway malignancies reported the major adverse effect was skin photosensitivity; other complications included mild hemoptysis, cough, chest discomfort, tracheal-esophageal fistula, and airway obstruction by tumor debris [18]. The overall morbidity rates were between 6-8% [16]. Post-PDT-related airway obstruction is a major complication, especially in patients with poor pulmonary function. Toilet bronchoscopy (usually rigid bronchoscopy) performed 1 to 3 days after PDT to prevent airway obstruction is recommended [17]. Tracheal stenosis has been reported, but no incidence rate or peak timing of the occurrence of stenosis has been reported. In our case, a good treatment response was observed after PDT. However, the patient also suffered from acute airway obstruction and subacute tracheal stenosis.

In conclusion, primary tracheal cancer is rare and the diagnosis is usually delayed. PDT provides an alternative treatment choice for patients who are not suitable for surgery. Acute airway obstruction and tracheal stenosis after treatment may occur and need close monitoring and emergency management.

References

1. Macchiarini P. Primary tracheal tumours, Lancet Oncol 2006; 7: 83-91.
2. Ahn Y, Chang H, Lim YS, *et al*. Primary tracheal tumors, review of 37 cases. J Thorac Oncol 2009; 4: 635-8.
3. Gaissert HA, Grillo HC, Shadmehr MB, *et al*. Long-term survival after resection of primary adenoid cystic and squamous cell carcinoma of the trachea and carina. Ann Thorac Surg 2004; 78: 1889-97.
4. Lewis JS Jr. p16 immunohistochemistry as a stand-alone test for risk stratification in oropharyngeal squamous cell carcinoma. Head Neck Pathol 2012; 6 Suppl 1: S75-82.
5. Bhattacharyya N. Contemporary staging and prognosis for primary tracheal malignancies: a population-based

analysis. Otolaryngol Head Neck Surg 2004; 131: 639-42.

6. Thotathil ZS, Agarwal JP, Shrivastava SK, *et al*. Primary malignant tumors of the trachea – the Tata Memorial Hospital experience. Med Princ Pract 2004; 13: 69-73.
7. Kurimoto N. Chapter 3. Diagnosis of depth penetration in the tracheobronchial tree, Endobronchial Ultrasonography, 1st ed, Japan, KINPODO, 2001; 30-8.
8. Honings J, Gaissert HA, van der Heijden HF, *et al*. Clinical aspects and treatment of primary tracheal malignancies. Acta Otolaryngol 2010; 130: 763-72.
9. Martin LK, Otterson GA, Bekaii-Saab T. Photodynamic therapy (PDT) may provide effective palliation in the treatment of primary tracheal carcinoma: a small case series. Photomed Laser Surg 2012; 30: 668-71.
10. Dougherty TJ, Kaufman JE, Goldfarb A, *et al*. Photoradiation therapy for the treatment of malignant tumors. Cancer Res 1978; 38(8): 2628-35.
11. McCaughan JS Jr, Williams TE. Photodynamic therapy for endobronchial malignant disease: A prospective fourteen-year study. J Thorac Cardiovasc Surg 1997; 114: 940-6; discussion 946-7.
12. Moghissi K. Role of bronchoscopic photodynamic therapy in lung cancer management. Curr Opin Pulm Med 2004; 10; 256-60.
13. Simone CB, 2nd, Friedberg JS, Glatstein E, *et al*. Photodynamic therapy for the treatment of non-small cell lung cancer. J Thorac Dis 2012; 4; 63-75.
14. Fujimura S, Sakurada A, Sagawa M, *et al*. A therapeutic approach to roentgenographically occult squamous cell carcinoma of the lung. Cancer 2000; 89; 2445-8.
15. Mason RJ, Broaddus VC, Martin T, *et al*. Chapter 22. Flexible Bronchoscopy, Murray and Nadel's Textbook of Respiratory Medicine, 5th Edition, United States, Saunder, 2010.
16. Ross P Jr. Photodynamic therapy for airway malignancies: the Ohio State University experience since 1998. J Natl Compr Canc Netw, 2012; 10: S9-13.
17. Chang YC, Lee JM, Ko WJ, *et al*. Airway obstruction following bronchoscopic photodynamic therapy in early centrally located lung cancer requiring extracorporeal membrane oxygenation. J Formos Med Assoc 2013; 112: 54-6.
18. Maziak DE, Markman BR, MacKay JA, *et al*. Photodynamic therapy in non-small cell lung cancer: a systematic review. Ann Thorac Surg 2004; 77: 1484-91.

原發性氣管內鱗狀細胞癌－以氣管環狀侵犯爲表現並接受光動力療法治療

張立禹 * 梁勝鎧 ** 許嘉林 * 李章銘 *** 余忠仁 *

原發性的氣管腫瘤非常罕見，其診斷往往需要倚賴電腦斷層掃瞄。本篇病例報告一位 50 歲女性病患，主訴慢性咳嗽約一年。胸部 X 光及電腦斷層皆無發現異常。支氣管鏡檢查發現瀰漫性且呈環狀侵犯的氣管內乳突瘤狀病灶，而支氣管鏡超音波檢查發現此病灶已侵犯超越基底膜的範圍。該病灶的病理切片結果為鱗狀細胞癌。病患接受光動力療法做為第一線治療且初步獲得不錯的腫瘤治療反應。*(胸腔醫學 **2014; 29: 218-223**)*

關鍵詞：鱗狀細胞癌，氣管腫瘤，支氣管鏡，支氣管鏡超音波，光動力療法

* 臺灣大學附設醫院 內科部，** 臺灣大學附設醫院新竹分院 內科部，*** 臺灣大學附設醫院 外科部
索取抽印本請聯絡：許嘉林醫師，臺灣大學附設醫院 內科部，台北市中山南路 7 號

Upper Airway Obstruction and Tracheal Perforation Caused by Thyroid Involvement of Disseminated Mucormycosis

Kai-Ping Chang, Tzu-Hsiu Tsai, Chong-Jen Yu

Thyroid fungal infection is extremely rare because the thyroid gland possesses a well-developed capsule, rich vasculature and high iodine content. We report a case of disseminated mucormycosis involving the thyroid gland, which caused catastrophic upper airway obstruction and tracheal perforation. This 57-year-old man with chronic myeloid leukemia had taken immunosuppressive agents for the treatment of graft-versus-host disease, which occurred after allogenic peripheral blood stem cell transplantation and donor lymphocyte infusion. The initial presentations of thyroid mucormycosis included fever, a painful neck mass and transient hyperthyroidism, with the imaging study showing a cystic lesion occupying the left thyroid gland. With extension of the thyroid abscess, the clinical course became complicated with upper airway obstruction, palsy of the left vocal cord, tracheal perforation and pulmonary infection. The diagnosis of disseminated mucormycosis involving the thyroid gland was made on the basis of histopathology of neck debrided tissue and biopsy of concomitant skin lesions, which disclosed non-septated and right-angle branching hyphae conforming to the morphology of mucormycosis. Despite treatment with antifungal agents, as well as intensive surgical debridement and reconstruction, he eventually succumbed to progressive pulmonary infection and deterioration of his hemodynamic status. Our case emphasizes the requirement of intensive monitoring and management of airway compromise, in addition to surgical debridement and systemic antifungal therapy, for the treatment of thyroid mucormycosis. The dismal prognosis and difficulty in diagnosis of this disease highlight the importance of a high index of suspicion regarding the presence of risk factors, and early invasive tissue sampling for histological and microbiological analyses. ***(Thorac Med 2014; 29: 224-232)***

Key words: mucormycosis, thyroid abscess, upper airway obstruction, tracheal perforation

Introduction

Mucormycosis is an emerging infectious disease caused by the ubiquitous filamentous fungi of the *Mucorales* order. It is the third most common invasive fungal infection in patients

Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan
Address reprint requests to: Dr. Tzu-Hsiu Tsai, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan

with hematological malignancies and allogeneic stem cell transplantation, in order of importance after candidiasis and aspergillosis [1-2]. The predisposing factors for mucormycosis in patients with hematologic malignancies and stem cell transplantation are prolonged neutropenia, use of high-dose systemic corticosteroid, high-risk stem cell transplantation (e.g., allogenic mismatched unrelated donor), severe graft-versus-host disease (GVHD) and its treatment, diabetes mellitus, previous exposure to Aspergillus-active antifungal agents (especially voriconazole), and relapsed leukemia [3-4]. Mucormycosis often manifests in a rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, or disseminated form [5], but thyroid gland involvement in mucormycosis is extremely rare. To the best of our knowledge, there are only 10 cases reported in the literature [6-14]. In this report, we present the case of a patient with chronic myeloid leukemia who had suffered from GVHD after donor lymphocyte infusion and allogeneic stem cell transplantation. Upper airway obstruction and tracheal perforation were complicated in this case due to extensive necrotizing infection of the thyroid gland caused by disseminated mucormycosis.

Case Report

This 57-year-old man was diagnosed with chronic myeloid leukemia in 2010, with bone marrow examination revealing t(9,22)(q34;q11). He had been initially treated with imatinib (Glivec®), with a poor response, and therefore was transferred to our hospital. Peripheral blood stem cell transplantation (PBSCT) from an allogeneic mismatched unrelated donor was carried out in December 2010. Because of disease relapse, he received a donor lymphocyte infusion in May 2011, along with an increased dose of imatinib. However, acute GVHD, which presented as cutaneous (grade 4), oral (grade 4), gastrointestinal (grade 1), and ocular (grade 2) involvement, developed 1 month after donor lymphocyte infusion. Immunosuppressive therapy, including pulse corticosteroid, cyclosporine, mycophenolate mofetil and tacrolimus, was administered for the treatment of GVHD.

Fever and enlargement of a neck mass were noted about 1 month after the development of GVHD. On local examination, there was tender swelling in the anterior part of the neck, predominantly on the left side. The overlying skin was erythematous and indurated. Routine investigations were unremarkable, except the following: white blood cell (WBC) count, 3780/μl with 89% neutrophils; hemoglobin (Hb), 8.4 g/dl; platelets, 15000/μl; aspartate transaminase (AST), 51U/L (normal range, <36 U/L). Thyroid function tests were indicative of hyperthyroidism (free T4, 2.74 ng/dL [normal range, 0.89-1.79 ng/dL]; T4, 13.5 μg/dL [normal range, 4.6-12.4 μg/dL]; T3, 102 ng/dL [normal range, 78-182 ng/dL]; and TSH, <0.1 μIU/mL [normal range, 0.39-4.2 μIU/mL]), whereas TSH receptor antibodies were negative. Ultrasound examination of the neck showed enlargement of the left lobe of the thyroid gland, which contained a hypoechoic cystic lesion. Meanwhile, magnetic resonance imaging of the neck revealed that the cystic lesion, measuring 5.3×4.5×6.0 cm in size, had rim enhancement, suggesting the presence of a thyroid abscess (Figure 1A). Initial blood culture yielded group B Salmonella, and tests for both serum Aspergillus galactomannan antigen and Cryptococcus antigen were reported negative. With the impression of acute thyroiditis and thyroid abscess, possibly caused by disseminated Salmo-

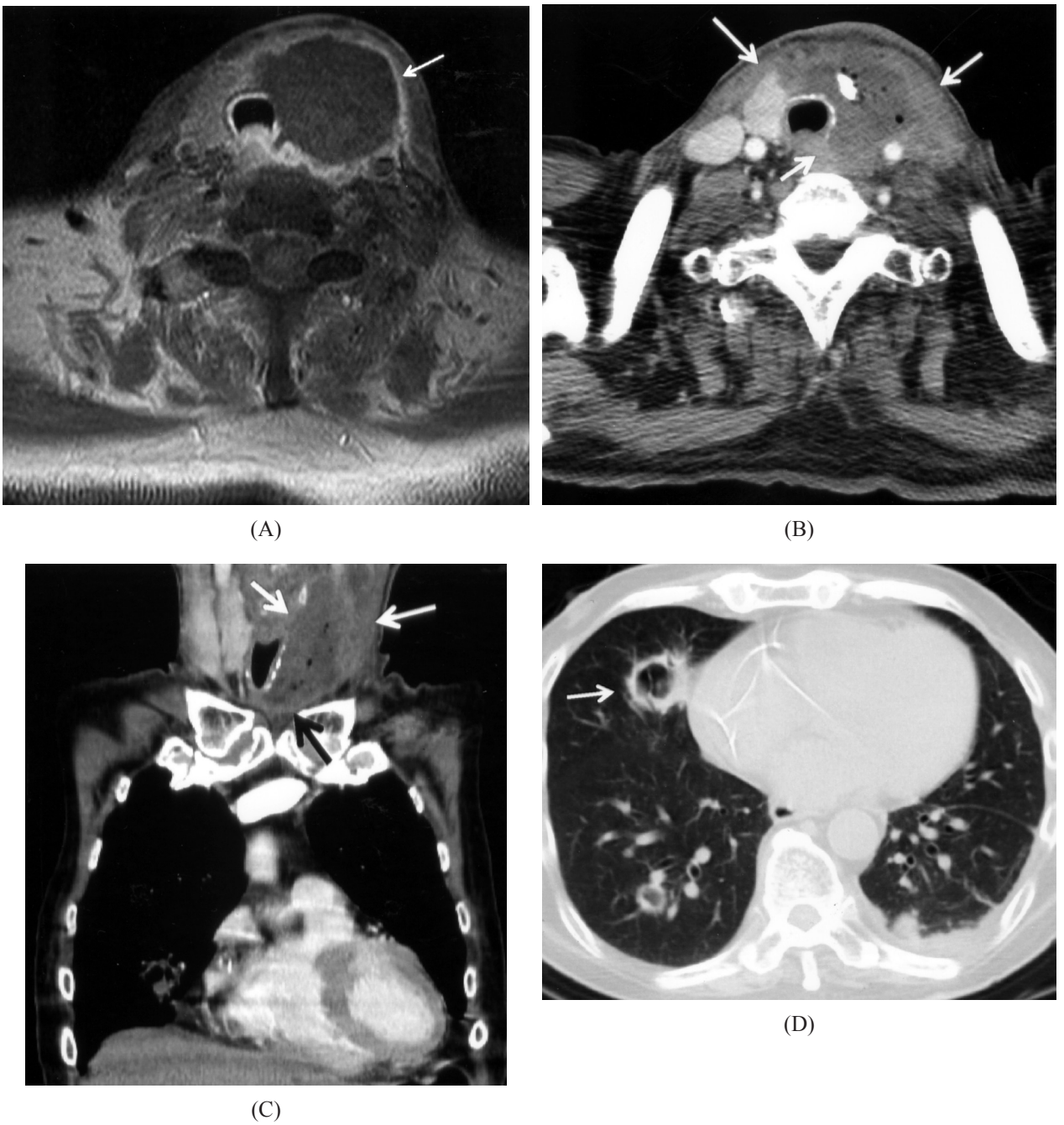


Fig. 1. (A) Magnetic resonance imaging of the neck at presentation reveals a rim-enhancing cystic lesion at the left lobe of the thyroid gland, measuring 53×45×60 mm in size (arrow). The trachea was pushed to the right side. (B) Computed tomography (CT) of the neck 2 weeks later showed left thyroid abscess (arrow) with air pockets after incision and tube drainage. The surrounding wall of the abscess is interrupted. (C) Coronal view discloses extension of the thyroid abscess to the deep neck. (D) CT of the chest also shows multiple cavitary nodules and consolidations at the bilateral lungs.

nella infection, ceftriaxone was administered, and incision and drainage of the thyroid abscess was performed. A drainage tube was placed after the operation, with drainage of serosangui-

nous fluid from the thyroid abscess in the following days. Bacterial culture of the drainage fluid yielded *Citrobacter freundii*.

Fever persisted despite treatment with ceftriaxone and tube drainage of the thyroid abscess. Escalation of antibiotic therapy with cefepime was begun, but the general condition of the patient deteriorated in the following days, with the presentation of progressive enlargement of the neck mass and dyspnea. Stridor was noted later, and laryngoscopy disclosed palsy of the left vocal cord. Multiple patchy opacities appeared simultaneously on the chest roentgenogram. Intubation and mechanical ventilation were begun immediately due to respiratory distress, oxygen desaturation and hypercapnia. Computed tomography of the neck and chest disclosed extension of the thyroid abscess, which significantly compressed the trachea (Figures 1B and 1C), as well as multiple cavitary lesions of the bilateral lung parenchyma (Figure 1D). Meanwhile, necrotic maculo-papular skin lesions with central gangrenous change appeared on the right thigh and leg, and were suspected to be the manifestation of septic embolization (Figure 2).

Surgical debridement with wide excision involving the deep neck was performed, and an antifungal agent with amphotericin-B (1.0 mg/kg/day) was added empirically due to the suspicion of disseminated fungal infection. Biopsy of the necrotic skin lesions was also done, as well as tissue culture of the necrotic skin tissue. Histopathology of the thyroid abscess and skin biopsy revealed non-septated and right-angle branching hyphae, conforming to the morphology of mucormycosis (Figures 3A and 3B). The diagnosis of disseminated mucormycosis with at least thyroid and cutaneous involvement was eventually made on the basis of pathological findings, although the fungal cultures from the debrided thyroid and skin tissues were negative. The dosage of amphotericin-B was adjusted to 1.5 mg/kg/day and was later changed to liposomal amphotericin-B (6 mg/kg/day). In the following days, air leakage from the trachea was noted and there was a visible tracheal perforated lesion surrounded by necrotic tissue (Figure 4). Tracheostomy was performed after excision of the tracheal perforation. A second debridement of the neck along with reconstruction with pectoris major muscle was executed. Pathology of peritracheal tissue also disclosed non-septated, right-angle branching hyphae. Despite treatment with broad-spectrum antibacterial and antifungal agents, as well as intensive surgical debridement of the thyroid abscess, the patient's condition continued to decline. He succumbed eventually to progressive pulmonary infection and deterioration of his hemodynamic status.

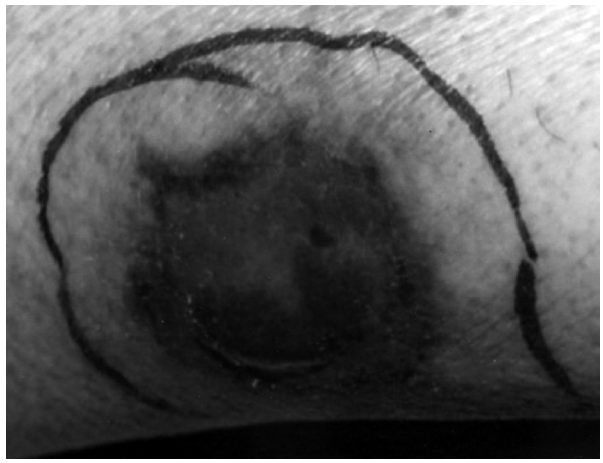
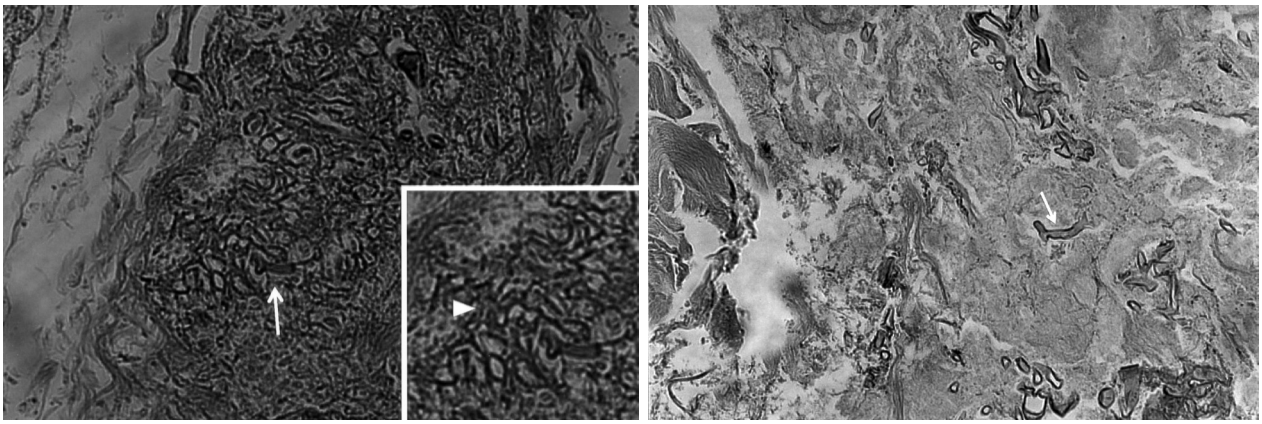


Fig. 2. Skin lesions concomitant with the thyroid abscess, which present as multiple erythematous maculo-papular lesions with central gangrenous change on the right lower extremity.

Discussion

The thyroid gland is resistant to infection



(A) (B)

Fig. 3. (A) Histopathology of the debrided neck tissue (periodic acid Schiff stain 400X) discloses non-septated fungal hyphae with right-angle branching (arrow), conforming to the morphology of mucormycosis. Superficial inflammatory cell infiltration and adipose tissue necrosis are also noted. (B) Histopathology of skin biopsy (periodic acid Schiff stain 400X) shows similar fungal hyphae (arrow). The background presents necrosis and inflammatory lymphocyte infiltration.

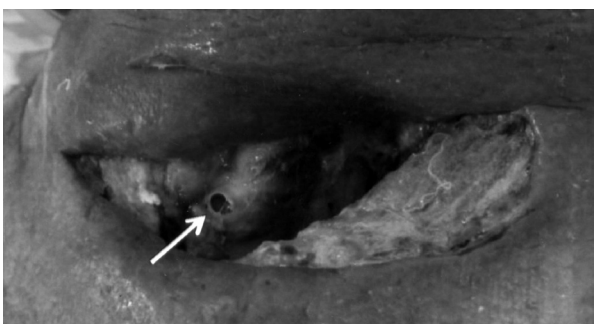


Fig. 4. A well-defined hole (arrow), measuring 2 mm in diameter, is noted on the left lateral side of the trachea, along with inflammatory tissue adjacent to the trachea and perforated lesion.

because of its well-developed capsule, rich lymphatic and vascular supply, and high iodine content. With the widespread usage of antibiotics in modern medicine, infection involving the thyroid gland is rare. A review of published reports from 1980 on demonstrated that Gram-positive bacteria (Staphylococcus and Streptococcus species) is the most common cause of thyroid abscess, although there have been cases in the literature caused by mycobacteria, Salmonella species and anaerobes [15]. Fungal infection of the thyroid gland is extremely uncommon, with most reports concerning systemic infections in immunocompromised hosts. By far, Aspergillus is the most common cause of fungal thyroiditis [16], followed by *Pneumocystis jiroveci* [17] and Cryptococcus [18]. Mucormycosis is a rarer cause of necrotizing thyroid infection due to fungi. Of the 10 cases of thyroid mucormycosis reported in the literature, only 1 involved an immunocompetent patient [8]; the other cases included 4 patients with hematological malignancy [6,13-14], 2 solid organ transplantation recipients [11-12], 1 patient with myelodysplastic syndrome receiving desferioxamine therapy [10], 1 with rapid progressive glomerulonephritis (RPGN) receiving immunosuppressive therapy [7], and 1 with acquired immunodeficiency syndrome (AIDS) [9]. Disseminated mucormycosis involving the thyroid is still associated with a dismal prognosis. Eight of the 10 patients mentioned above and our case succumbed due to the disseminat-

ed infection, and diagnosis of the disease was often made *postmortem* [14].

In all the above cases with thyroid involvement of mucormycosis, there was no mention of upper airway compromise. To the best of our knowledge, there were only 2 reported cases in which the upper airway, other than the nasal cavity, was obstructed due to mucormycosis. The first case was mucormycosis of the trachea in a young patient with diabetes mellitus [19]. The other was laryngeal mucormycosis with retropharyngeal abscess [20]. Both cases involved isolated mucormycosis without dissemination, and a full recovery was achieved after surgical debridement and appropriate antifungal therapy. By contrast, our patient presented with upper airway obstruction caused by necrotizing infection extending from the thyroid mucormycosis, which resulted in palsy of the left vocal cord, compression of the trachea, and even tracheal perforation. Our case illustrated the risk of airway compromise in patients with thyroid mucormycosis, and highlighted the requirement of intensive monitoring and management of respiratory complications, in addition to aggressive surgical debridement and systemic antifungal therapy.

The diagnosis of invasive mold infection is problematic and is often delayed due to the nonspecific manifestations. The clinical symptoms and local signs of fungal infections involving the thyroid gland are indistinguishable from those of other causes of infectious thyroiditis, which could include fever, anterior cervical pain, and thyroid enlargement sometimes associated with dyspnea and dysphagia. Laboratory features of transient hyperthyroidism, as found in our case, due to the release of thyroid hormone from follicular cells followed by residual hypothyroidism, also have been described. Cultures of blood are nearly always negative for the etiologic pathogens, and cultures from the infectious site are often suboptimal. Furthermore, there are no biomarkers to specifically identify mucormycosis, and radiographic findings in diseases caused by Mucorales and Aspergillus were often similar. Establishment of the specific diagnosis in fungal thyroiditis is usually achieved by obtaining tissue for histologic or cultural confirmation, with which the non-septated and right-angle branching fungal hyphae characteristics of mucormycosis could be histologically revealed. It is worth noting that, and as observed in this case, even when fungal hyphae are seen in the histopathological analysis, microbiologic cultures might be positive in only half of all cases [4,21]. Thus, the index of suspicion for this disease with a dismal prognosis should be very high in the presence of risk factors, and an early invasive procedure for appropriate tissue sampling might be important to make the diagnosis *antemortem*, and as soon as possible.

Early diagnosis, reversal of predisposing factors, appropriate antifungal therapy (such as amphotericin-B, including the lipoid form), and adequate surgical debridement are crucial to improve the outcome for these patients. Mucormyces are resistant to voriconazole, which is active against Aspergillus. Liposomal amphotericin-B has advantages over amphotericin-B in the treatment of mucormycosis due to (a) better central nervous system penetration, (b) more reduction in the fungal burden, (c) immunomodulatory effects, and (d) less nephrotoxicity, and thus may be considered as a first-line antifungal agent [5]. However, tissue necrosis, angioinvasion, and thrombosis may lead to poor penetration of antifungal agents. Thus, surgery plays a crucial role in the treatment of mucor-

mycosis, and has been shown to be independently associated with treatment success and survival [22]. The overall mortality rate is still high, particularly in patients with disseminated disease and stem cell transplantation recipients, reaching more than 90% [3].

In conclusion, to the best of our knowledge the index case described herein represents the first reported case of disseminated mucormycosis presenting as acute thyroiditis that resulted in upper airway obstruction and tracheal perforation. This case and a review of previous reports suggest that the thyroid should be added to the list of tissues that can be the site of infection in immunocompromised patients with disseminated mucormycosis, and that severe airway compromise might ensue.

References

1. Pagano L, Caira M, Candoni A, *et al*. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 2006; 91(8): 1068-75.
2. Marr KA, Carter RA, Crippa F, *et al*. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002; 34(7): 909-17.
3. Roden MM, Zaoutis TE, Buchanan WL, *et al*. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41(5): 634-53.
4. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood 2011; 118(5): 1216-24.
5. Sun HY, Singh N. Mucormycosis: its contemporary face and management strategies. Lancet Infect Dis 2011; 11(4): 301-11.
6. Chiba N, Miki R. [Zygomycosis caused by Cunninghamella bertholletiae]. Rinsho Byori 1990; 38(11): 1219-25.
7. Vessely MB, Zitsch RP, 3rd, Estrem SA, *et al*. Atypical presentations of mucormycosis in the head and neck. Otolaryngol Head Neck Surg 1996; 115(6): 573-7.
8. Solano T, Atkins B, Tambosis E, *et al*. Disseminated mucormycosis due to *Saksenaea vasiformis* in an immunocompetent adult. Clin Infect Dis 2000; 30(6): 942-3.
9. Fujii T, Takata N, Katsutani S, *et al*. Disseminated mucormycosis in an acquired immunodeficiency syndrome (AIDS) patient. Intern Med 2003; 42(1): 129-30.
10. Kubota N, Miyazawa K, Shoji N, *et al*. A massive intraventricular thrombosis by disseminated mucormycosis in a patient with myelodysplastic syndrome during deferoxamine therapy. Haematologica 2003; 88(11): EIM13.
11. Saikia UN, Jain D, Joshi K, *et al*. Disseminated zygomycosis presenting as thyroid abscess in a renal allograft recipient. Nephrol Dial Transplant 2007; 22(2): 641-4.
12. Minet C, Bonadona A, Tabah A, *et al*. Non-fatal disseminated mucormycosis in a solid organ transplant. Rev Mal Respir 2009; 26(9): 998-1002.
13. Mayayo E, Klock C, Goldani L. Thyroid involvement in disseminated zygomycosis by *Cunninghamella bertholletiae*: 2 cases and literature review. Int J Surg Pathol 2011; 19(1): 75-9.
14. Irga N, Kosiak W, Jaworski R, *et al*. Hyperthyroidism secondary to disseminated mucormycosis in a child with acute lymphoblastic leukemia: case report and a review of published reports. Mycopathologia 2013; 175(1-2): 123-7.
15. Jacobs A, Gros DA, Gradon JD. Thyroid abscess due to Acinetobacter calcoaceticus: case report and review of the causes of and current management strategies for thyroid abscesses. South Med J 2003; 96(3): 300-7.
16. Goldani LZ, Zavascki AP, Maia AL. Fungal thyroiditis: an overview. Mycopathologia 2006; 161(3): 129-39.
17. Zavascki AP, Maia AL, Goldani LZ. Pneumocystis jiroveci thyroiditis: report of 15 cases in the literature. Mycoses 2007; 50(6): 443-6.
18. Klock C, Cerski M, Goldani LZ. Histopathological aspects of neurocryptococcosis in HIV-infected patients: autopsy report of 45 patients. Int J Surg Pathol 2009; 17(6): 444-8.
19. Schwartz JR, Nagle MG, Elkins RC, *et al*. Mucormycosis of the trachea: an unusual cause of acute upper airway obstruction. Chest 1982; 81(5): 653-4.
20. Alkan S, Kosar AT, Ozkaya I, *et al*. Coexistence of laryngeal mucormycosis with retropharyngeal abscess causing acute upper airway obstruction. J Otolaryngol Head Neck Surg 2008; 37(3): E73-5.
21. Tarrand JJ, Lichterfeld M, Warraich I, *et al*. Diagnosis of invasive septate mold infections. A correlation of micro-

biological culture and histologic or cytologic examination. Am J Clin Pathol 2003; 119(6): 854-8.
22. Lee FY, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. Arch Intern Med 1999; 159(12): 1301-9.

彌漫性毛黴菌病侵犯甲狀腺引起之上呼吸道阻塞與氣管破裂

張凱坪　蔡子修　余忠仁

甲狀腺的黴菌感染相的罕見因為它有結構良好的被膜包覆及擁有豐富的血管及高濃度的碘。我們在此提出一個彌漫性毛黴菌感染併甲狀腺侵犯造成嚴重上呼吸道阻塞及氣管穿孔的個案。這位 57 歲慢性髓性白血病（chronic myeloid myeloma）男性病患因週邊血液幹細胞移植（peripheral stem cell transplantation）及移植供應者淋巴球輸注（donor lymphocyte infusion）治療後的移植物抗宿主病（graft-versus-host disease）而服用免疫抑制劑。甲狀腺毛黴菌感染初始表現為發燒、疼痛的頸部腫塊、及暫時性甲狀腺亢進與影像學顯示左甲狀腺囊腫。因甲狀腺膿瘍的擴展，臨床進展成左側聲帶麻痺、氣管穿孔及肺部感染。彌漫性毛黴菌感染的診斷是基於頸部清創組織及皮膚切片的病理學表現為非分隔及有直角分枝的菌絲。雖然以抗黴菌藥及積極的手術清創和重建，病人仍因肺部感染進展及血循惡化而死亡。這個個案強調在治療甲狀腺毛黴菌感染時積極的監測和處理呼吸道的併發症和手術清創及抗黴菌藥的必要性。進一步地，疾病的不佳預後及困難診斷也突顯在高風險病患臨床懷疑及早期侵入性組織診斷的重要性。***(胸腔醫學 2014; 29: 224-232)***

關鍵詞：毛黴菌病，甲狀腺膿瘍，上呼吸道阻塞，氣管穿孔

國立臺灣大學附設醫院　內科部　胸腔內科
索取抽印本請聯絡：蔡子修醫師，國立台灣大學醫學院附設醫院　內科部　胸腔內科，台北市中山南路 7 號

Surgery of Triple Synchronous Lung Cancer with Different Cell Types as Demonstrated by ^{18}F-FDG PET Imaging

Yuan-Ming Tsai*, Tsai-Wang Huang*, Chung-Kan Peng**, Yu-Chieh Lin***, Lin-Fan Lin****, Shih-Chun Lee*

Synchronous multiple primary lung cancer (MPLC) is presumed to be an uncommon entity. In the absence of easily available genetic or molecular markers, the differentiation between MPLC and isolated pulmonary metastasis will remain difficult in a clinical setting, leading to controversies regarding management considerations. We present a rare case of synchronous MPLC with differences in ^{18}F-FDG avidity on positron emission tomography–computed tomography imaging. We also share our experience with its diagnosis, management, and histopathological results. ***(Thorac Med 2014; 29: 233-237)***

Key words: lung cancer, synchronous, PET/CT, surgery, histology

Introduction

Lung cancer is the leading cause of cancer-related death [1], and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is recommended as standard work-up for lung cancer staging [2]. It is often difficult for thoracic surgeons to distinguish between synchronous primary lung cancers and metastatic disease. Metastatic lung cancer is treated with palliative methods, but synchronous multiple primary lung cancer (MPLC) with node-negative disease is managed aggressively because survival is similar to that of solitary primary lung cancer [2]. Although ^{18}F-FDG PET can help identify malignant lung lesions and suggest distinct tumor histologies [3], the preoperative definite diagnosis, differentiation and management remain a challenge with the evolution of the pathologic classification of non-small cell lung cancer.

Case Report

A 70-year-old woman presented with intermittent productive cough and exertional dyspnea for 1 month. She had no smoking history and the main comorbidity was arterial hypertension. On physical examination, breathing sounds were slightly decreased at the left

*Division of Thoracic Surgery, Department of Surgery; **Division of Pulmonary Medicine, Department of Medicine; ***Department of Pathology; ****Department of Nuclear Medicine, Tri-Service General Hospital, National Defense Medical Center, Taiwan, R.O.C.
Address reprint requests to: Dr. Shih-Chun Lee, Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital, No. 325, Section 2, Cheng-Kung Road, Taipei 114, Taiwan, R.O.C.

thorax. Chest X-ray revealed 2 nodules located in the left lung field. Computed tomography (CT) of the chest showed the presence of a tumor at the left main bronchus and 2 nodules in the left lung. PET/CT revealed 2 areas of high-intensity FDG uptake within the left lung; a 1.3-cm tumor with a SUVmax of 9.5 was observed in the left main bronchus (Figure 1A) and a 1.0-cm soft tissue opacity with a SUVmax of 8.8 was seen in the left upper lobe (Figure 1B). Another 1.4-cm nodule without FDG uptake was noted in the left lower lobe (Figure 1C). No lymphadenopathy was identified. Flexible bronchoscopy was performed and confirmed squamous cell carcinoma of the left main bronchus. CT-guided transthoracic biopsy of soft tissue opacity in the left upper lobe was done to confirm adenocarcinoma, but it was difficult to achieve a definitive diagnosis of the nodule in the left lower lobe. There were no pathological changes in the ECG, echocardiography and abdominal sonography. Pulmonary function tests were acceptable for pneumonectomy. The multidisciplinary team decision was to perform left upper sleeve lobectomy if the nodule in the left lower lobe was found to be nonmalignant. The patient was informed of the possibility of pneumonectomy because of the malignancy in the left lower lobe. The operation was performed under general anesthesia with one-lung ventilation using a right double-lumen endotracheal tube, and the site was confirmed using a flexible bronchoscope. An anterolateral thoracotomy was performed through the 4th intercostal space. The intercostal muscles were dissected off long enough and a rib spreader was used to expose clearly the hilum and lateral aspect of the mediastinum. After finger palpation of the left lung, we found the tumor in the left lower lobe and resected it with the endostapler. Analysis of frozen sections of the wedge-resected nodule in the left lower lobe revealed adenocarcinoma with a bronchioalveolar pattern. The patient then underwent left pneumonectomy. Histo-

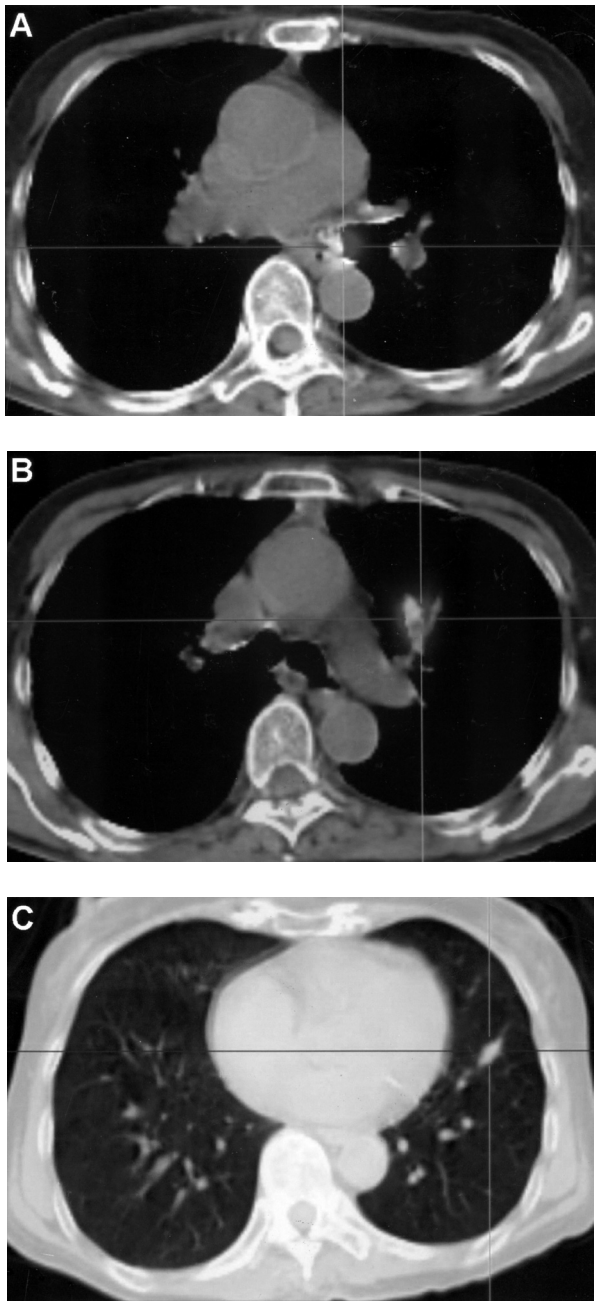


Fig. 1. PET/CT of the 3 areas in the left lung (A) A 1.3-cm left main bronchial mass with FDG uptake (SUVmax=9.5) (B) A 1.0-cm left upper lobe soft tissue opacity with FDG uptake (SUVmax=8.8) (C) A 1.4-cm left lower lobe nodule without FDG uptake

logical examination revealed that the bronchial lesion was a squamous cell carcinoma with an intercellular bridge, hyperchromatic nuclei and frequent mitotic figures (Figure 2A). The upper lobe lesion was a minimally invasive adenocarcinoma characterized by predominant adenocarcinoma in situ with focal minimal infiltration into the pulmonary stroma (Figure 2B), and the lower lobe lesion was an invasive adenocarcinoma with mixed acinous and lepidic tumor growth patterns (Figure 2C). No lymph node metastases and no epidermal growth factor receptor (EGFR) mutations were observed. The patient made a successful recovery following surgery, and no recurrence was found during the 9-month follow-up period.

Discussion

Multiple primary lung cancer (MPLC) occurs with an incidence of 0.2-20% [4]. It is difficult to make an appropriate diagnosis in patients with synchronous multiple primary lung nodules, and the best management for this condition remains controversial. Therefore, overlooking a possible curative treatment for MPLC should be avoided. Although PET/CT is a powerful tool for detecting and staging lung cancer, it may describe a low or absent FDG uptake in bronchioalveolar carcinoma (BAC) [3]. It is currently recommended that the term "BAC" should not be used [5]. Instead, the use of a new system of lung adenocarcinoma classification using resection specimens has been proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society [5]. Differences in histology for multiple pulmonary tumors are indicative of primary lung tumors [4]. The 3 lesions in this patient had different histologies. Squamous cell carcinoma was detected preoperatively in the left main bronchus using bronchoscopic biopsy. A lesion with high FDG uptake in the left upper lung lobe was

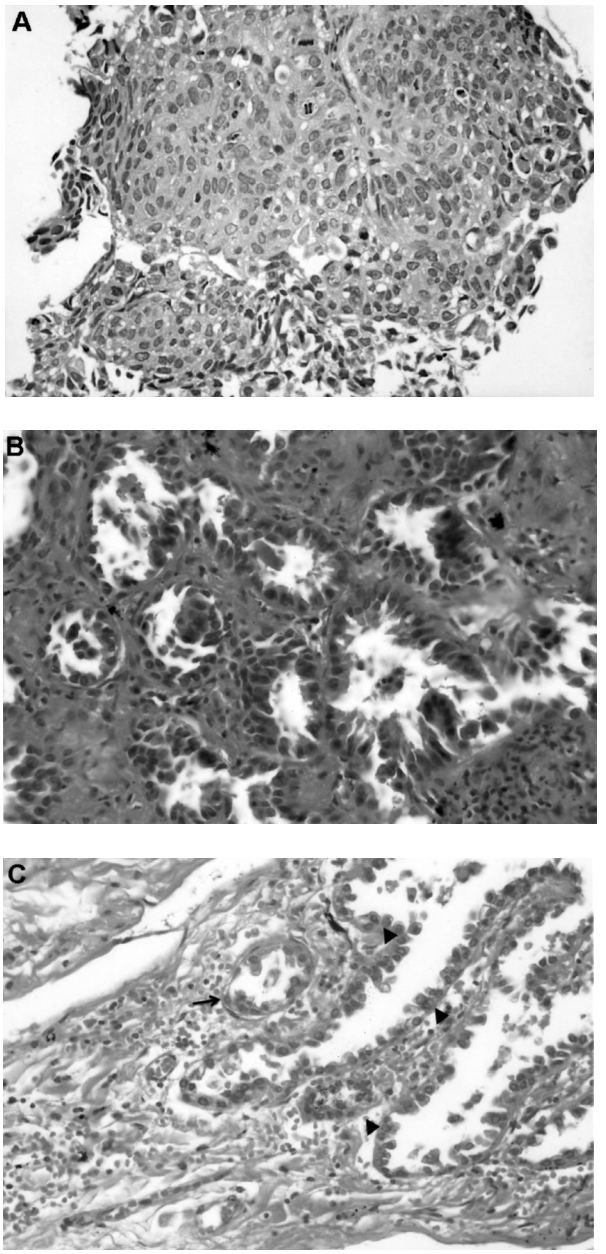


Fig. 2. Microphotography demonstrated (A) squamous cell carcinoma (H&E, X400) (B) minimally invasive adenocarcinoma with microscopic stromal invasion less than 5 mm (H&E, X400) (C) invasive adenocarcinoma with mixed acinar (arrow) and lepidic (arrow head) growth patterns (H&E, X400)

diagnosed as minimally invasive adenocarcinoma, and the other without FDG uptake in the left lower lung lobe was diagnosed intraoperatively as malignant. The final pathology was invasive adenocarcinoma. FDG uptake reflects the tumor metabolic activity, and values on PET images (SUVs) have been shown to increase with poorer tumor differentiation and more aggressive tumors [2]. However, the partial volume effect may lead to underestimation of SUVs of the small tumor [6] and large differences in SUVs between lung tumors in a single patient may be considered as second primary lung cancers, meaning they were potentially curable [2]. Surgical resection can be recommended if a better selection process is used to identify suitable patients (including cardiopulmonary function tests, PET scan, and mediastinoscopy to exclude node metastasis) [7]. To date, only 1 other case has been reported with 2 synchronous MPLC using PET/CT with both true-positive and false-negative findings [3]. Our case presented with 3 synchronous MPLC. The lesion with higher FDG uptake was found to be a minimally invasive adenocarcinoma, whereas the lesion with no FDG uptake was an invasive adenocarcinoma. We performed left pneumonectomy because complete resection has been reported to offer the best chance for prolonged survival as long as the mediastinal lymph node involvement is negative after an extensive work-up [7]. Surgical resection is safe, with low perioperative morbidity and mortality for patients with synchronous MPLC undergoing resection [8]. Samples of any suspicious nodules should be obtained for staging and guiding the therapeutic management of multiple lung cancer patients. To the best of our knowledge, this report is the first to describe the association of MPLC presenting with tumors of different cell types and PET scan. The patient survived without complications after surgical resection. Further molecular studies may be helpful to clarify the MPLC pathogenesis. In conclusion, differentiating MPLC and isolated pulmonary metastasis will remain difficult in a clinical setting. An aggressive staging work-up and meticulous surgery can result in long-term patient survival.

References

1. Molina JR, Yang P, Cassivi SD, *et al*. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008; 83: 584-94.
2. Dijkman BG, Schuurbiers OC, Vriens D, *et al*. The role of ^{18}F-FDG PET in the differentiation between lung metastases and synchronous second primary lung tumours. Eur J Nucl Med Mol Imaging 2010; 37: 2037-47.
3. Derlin T, Clauditz TS, Quaas A, *et al*. Synchronous bronchioloalveolar and squamous cell lung cancer with different ^{18}F-FDG avidity on PET/CT. Clin Nucl Med 2012; 37: 255-6.
4. Trousse D, Barlesi F, Loundou A, *et al*. Synchronous multiple primary lung cancer: an increasing clinical occurrence requiring multidisciplinary management. J Thorac Cardiovasc Surg 2007; 133: 1193-200.
5. Travis WD, Brambilla E, Noguchi M, *et al*. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011; 6: 244-85.
6. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. J Nucl Med 2007; 48: 932-45.
7. Voltolini L, Rapicetta C, Luzzi L, *et al*. Surgical treatment of synchronous multiple lung cancer located in a different lobe or lung: high survival in node-negative subgroup. Eur J Cardiothorac Surg 2010; 37: 1198-204.
8. Shah AA, Barfield ME, Kelsey CR, *et al*. Outcomes after surgical management of synchronous bilateral primary lung cancers. Ann Thorac Surg 2012; 93: 1055-60.

多重原發性肺癌在不同強度正子攝影顯影下之手術治療－個案報告

蔡遠明 * 黃才旺 * 彭忠衍 ** 林鈺傑 *** 林立凡 **** 李世俊 *

臨床上是否為轉移性肺腫瘤或均為原發性肺癌，因缺乏基因學上之分子標記，常造成診斷及治療上之困擾。70 歲女性，臨床表徵為持續咳嗽及漸進性喘，時間達一個月之久。經詳細檢查，正子攝影顯示左主支氣管及左肺上葉有腫塊顯影，左肺下葉有一 1.4 公分腫塊無顯影。支氣管鏡檢證實左主支氣管為鱗狀上皮細胞癌，左肺上葉及下葉腫瘤術後病理組織依新肺腺癌分類準則，分別為微侵犯性肺腺癌及侵犯性肺腺癌，然而術前的正子攝影呈高度顯影的左肺上葉腫塊，術後為微侵犯性肺腺癌；相反地，術前無正子攝影的左肺下葉腫塊，術後為侵犯性肺腺癌。*(胸腔醫學 **2014; 29: 233-237**)*

關鍵詞：肺癌，多重原發性，正子攝影，手術切除，病理組織

* 三軍總醫院 胸腔外科，** 三軍總醫院 胸腔內科，*** 三軍總醫院 病理部，**** 三軍總醫院 核子醫學部
索取抽印本請聯絡：李世俊醫師，三軍總醫院 胸腔外科，台北市內湖區成功路二段 325 號

An Unusual Case of Pulmonary Sarcomatoid Carcinoma (Subtype Spindle Cell Carcinoma) Presenting as Endobronchial Mass with Pulmonary Artery Invasion: A Case Report and Literature Review

Chia-Fu Hsu*, Wen-Pin Su**, Cheng-Lin Wu***, Chien-Chung Lin*, Yau-Lin Tseng****, Han-Yu Chang*

Pulmonary sarcomatoid carcinoma is a rare form of non-small cell lung cancer that comprises 0.1% to 0.4% of all lung malignancies. Patients are predominantly male smokers with a median age of 60 to 70 years. The clinical course is aggressive and the prognosis is significantly worse than that of other forms of non-small cell lung cancer. Pulmonary sarcomatoid carcinoma usually presents as a large, solitary, peripheral mass with chest wall invasion, and very rarely as a protruding endobronchial tumor with pulmonary vessel invasion. We report the case of a 59-year-old female non-smoker with the unusual presentation of pulmonary sarcomatoid carcinoma (subtype spindle cell carcinoma) as an endobronchial mass obstructing the left main bronchus and invading the left pulmonary artery. ***(Thorac Med 2014; 29: 238-245)***

Key words: spindle cell carcinoma, pulmonary sarcomatoid carcinoma

Introduction

Lung cancer is the most common cancer worldwide, based on the GLOBOCAN 2008 estimates [1]. Pulmonary sarcomatoid carcinomas are a poorly differentiated group of non-small cell lung cancers (NSCLCs) that contain sarcoma or sarcoma-like components [2]. Pulmonary sarcomatoid carcinomas comprise only 0.1% to 0.4% of all lung cancers [3]. According to the 2004 World Health Organization (WHO) classification of invasive malignant epithelial lung tumors, pulmonary sarcomatoid carcinomas consist of 5 major histological variants: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma [2]. Small biopsies do not usually show both the epithelial and sarcomatous components of the tumor, so they are easily misdiagnosed [4]. Pulmonary sarcomatoid carcinomas are more common in men and smokers, with a mean age of 65 years at diagnosis [5-8]. An exception is the pulmonary blastoma subtype, which usually affects men

Division of Pulmonary Medicine*, Division of Oncology**, Department of Internal Medicine, Department of Pathology***, Department of Surgery****, National Cheng Kung University Hospital, Tainan, Taiwan
Address reprint requests to: Dr. Han-Yu Chang, Division of Pulmonary Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng-Li Rd., Tainan 704, Taiwan

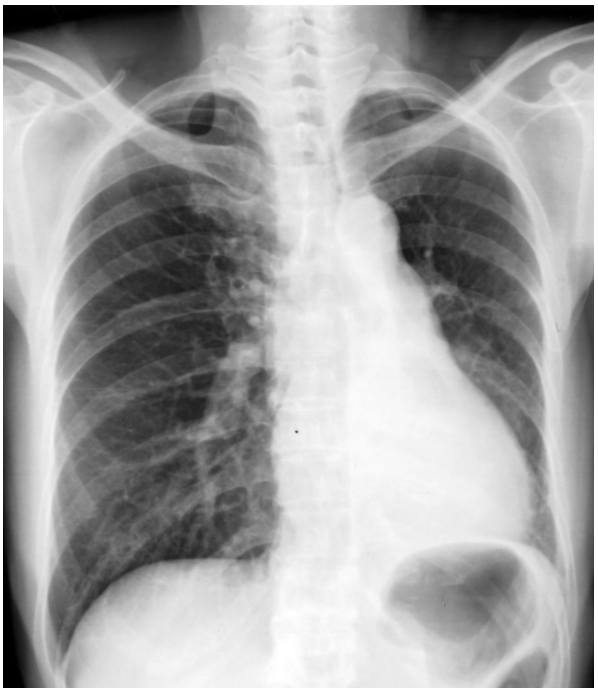
and women equally during the fourth decade of life [9]. Cough and hemoptysis are the most common presenting symptoms [10]. Compared with other NSCLCs, pulmonary sarcomatoid carcinomas are more aggressive in their clinical course. They are frequently symptomatic and locally advanced, with a high recurrence rate and poor survival rates [11]. Although pulmonary sarcomatoid carcinomas can grow peripherally or centrally, they usually present as a peripheral solitary mass with chest wall invasion, and more commonly in the upper lobes [5-6]. Herein, we report the case of a 59-year-old woman with pulmonary sarcomatoid carcinoma with the unusual presentation of an endobronchial mass obstructing the left main bronchus and invading the pulmonary artery.

Case Report

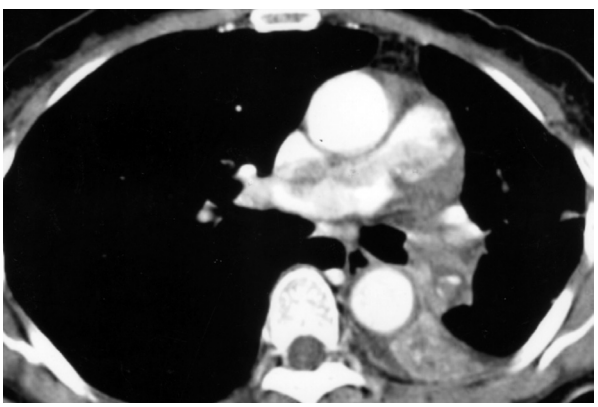
A 59-year-old non-smoking housewife presented with productive cough of 6 months' duration. During this period, several episodes of intermittent fever occurred. She also experienced mild dyspnea on exertion and had lost approximately 10 kg of body weight. She visited our chest outpatient department because of the chronic cough. Chest radiography showed left lower lobe collapse (Figure 1A). A computed tomography (CT) scan of her chest with contrast revealed a low-density complex mass filling the distal left main bronchus with left lower lobe collapse and invasion of the pulmonary trunk and left pulmonary artery (Figure 1B, 1C). Flexible bronchoscopy located a soft, movable, whitish, and irregular endobronchial mass within the left main bronchus (Figure 2A). Autofluorescence imaging videobronchoscopy showed scattered green spots without a purple surface (Figure 2B). An endobronchial biopsy was performed, but only necrotic tissue was noted. A rigid bronchoscopic biopsy was then undertaken to obtain larger specimens, and the pathological studies revealed necrotic tissue and malignant spindle cells with hyperchromatism (Figure 3A), as well as dyskeratotic cells and suppurative inflammation. The neoplastic cells were immunohistochemically positive for pancytokeratin (Figure 3B), which suggested an epithelial origin. Immunohistochemical staining of cluster of designation (CD) 31, CD34, thyroid transcription factor-1 (TTF-1), and p63 were all negative. Angiosarcoma was less likely based on the negative CD31 and CD34 findings, and a pulmonary sarcomatoid carcinoma (subtype spindle cell carcinoma) was diagnosed. Since the chest CT scan showed involvement of the mediastinum, great vessels and ipsilateral mediastinal lymph nodes, the clinical stage was determined to be T4N2M0, stage IIIB. The patient initially received concurrent chemoradiotherapy with vinorelbine. After approximately 8 weeks, the disease had progressed focally without distant metastasis; therefore, salvage chemotherapy with docetaxel and cisplatin was started. Five months later, the patient's disease status was stable.

Discussion

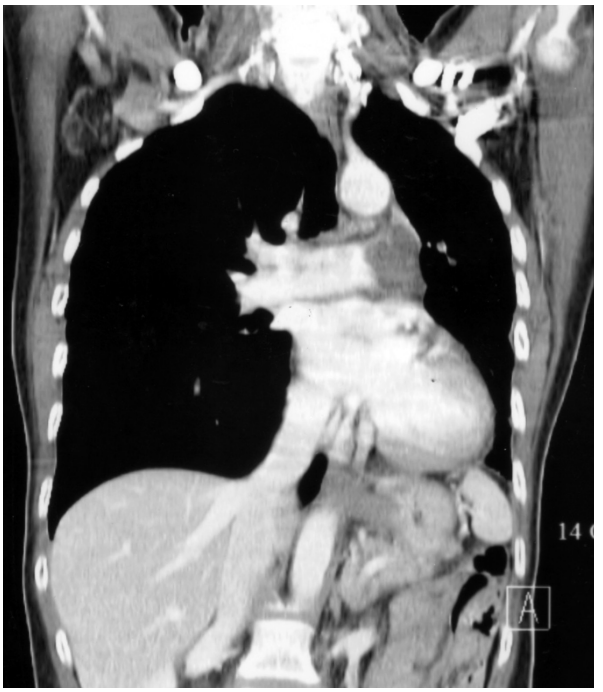
For many decades, there was no clinically practical consensus on pulmonary carcinomas containing variable amounts of sarcomatous or sarcomatoid elements. Clinicians encountered difficulties in unifying the terminology and classification for treatment planning and determining the prognosis until the 2004 WHO classification of lung cancers was published. The diagnosis of pulmonary sarcomatoid carcinomas is primarily determined by histologic



(A)



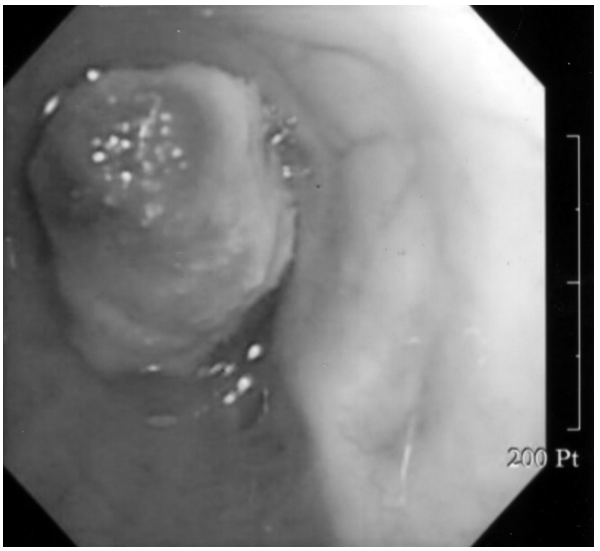
(B)



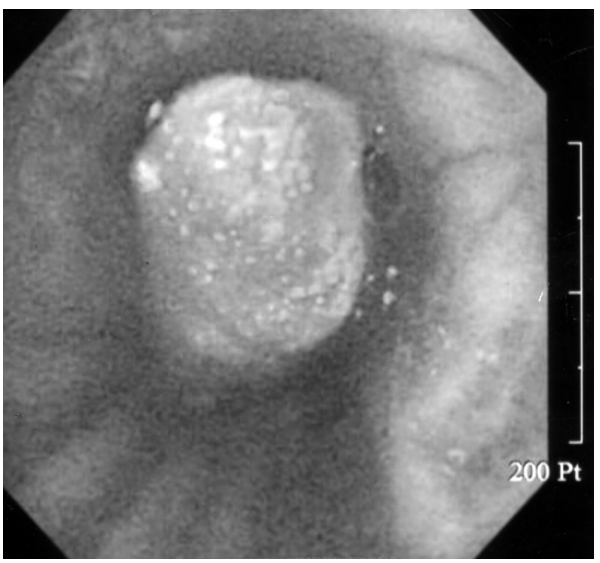
(C)

Fig. 1. Image findings of the pulmonary sarcomatoid carcinoma. (A) Chest radiography showed a left endobronchial tumor with left lower lobe collapse. (B) & (C) The transverse and coronal sections of contrast-enhanced chest CT revealed a mass filling the left main bronchus, invading the pulmonary trunk and left pulmonary artery.

features under light microscopy; however immunohistochemistry (IHC) may be needed in certain circumstances [2]. Although a diagnosis of pulmonary sarcomatoid carcinomas may be reached from small biopsy specimens, a large resection of the tumor is typically required for a definite diagnosis, because of the heterogeneity and pleomorphism [4]. Five subtypes of pulmonary sarcomatoid carcinomas exist: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma [2-3,12]. Pleomorphic carcinoma is a non-small cell carcinoma combined with spindle and/or giant cells (accounting for at least 10% of the tumor mass). Spindle cell carcinoma is comprised of only malignant spindle cells. In this setting, IHC stains for keratin should be taken to confirm the carcinoma diagnosis. Giant cell carcinoma is defined as a carcinoma consisting of bizarre pleomorphic giant cells

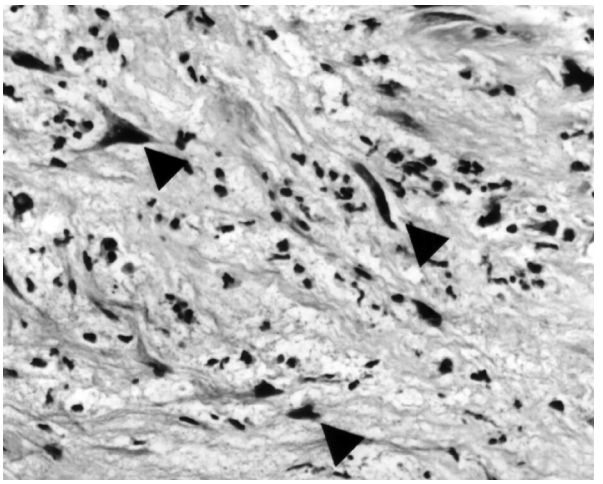


(A)

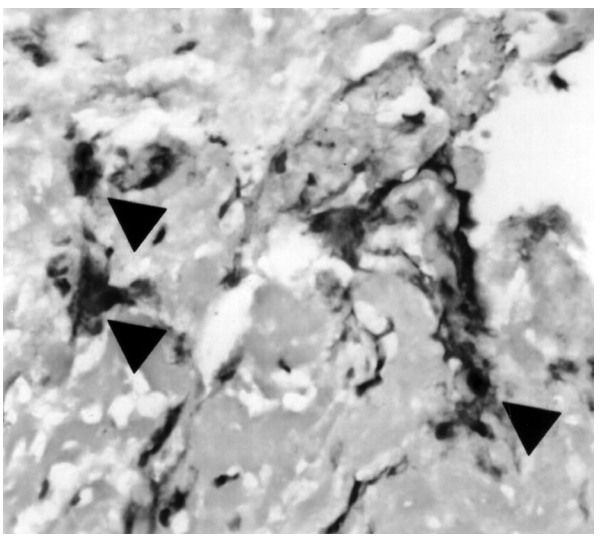


(B)

Fig. 2. Bronchoscopic findings of the pulmonary sarcomatoid carcinoma. (A) White light bronchoscopy revealed a whitish and irregular endobronchial mass within the left main bronchus. (B) Autofluorescence imaging videobronchoscopy showed multiple green spots scattered around the mass.



(A)



(B)

Fig. 3. Microscopic findings of the pulmonary sarcomatoid carcinoma (spindle cell carcinoma) (A) Hematoxylin and eosin staining (X200) revealed malignant spindle cells (arrowhead). (B) The immunohistochemical staining of pan-cytokeratin (X200) highlighted neoplastic cells (arrowhead).

only. Carcinosarcoma is a typical carcinoma combined with sarcomatous elements (cartilage, bone, or skeletal muscle). Pulmonary blastoma is a biphasic tumor with the appearance of fetal adenocarcinoma and a primitive mesenchymal stroma with blastematous cells, and occasionally has foci of true sarcomatous differentiation (osteosarcoma, chondrosarcoma, or rhabdomyosarcoma).

According to a review of case series, pulmonary sarcomatoid carcinomas are rare (<3%),

with a higher prevalence in males (the male-to-female ratio is approximately 3.8:1) and smokers, and an average age at presentation of 60 years [12]. However, pulmonary blastoma, the least common subtype, usually affects men and women equally during the fourth decade of life. The recent Surveillance, Epidemiology, and End Results (SEER) database study in the United States found that of 878,810 patients with lung cancer, only 3647 had been diagnosed with sarcomatoid carcinoma (0.4%) [13]. The demographics in the SEER study, including gender and age at presentation, were compatible with previous studies.

Giant and spindle cell carcinomas are the most common histologic types, and pulmonary blastomas are extremely rare. Associated symptoms usually include thoracic pain, cough, and hemoptysis [3]. Pleomorphic carcinomas and pulmonary blastomas often develop in the peripheral area. Pleomorphic carcinomas are more substantially involved in the chest wall and are observed in up to 25% of cases, whereas a central location is observed more often in cases of carcinosarcomas. The diameter of the tumors has been reported to range from 1 cm to 28 cm (mean: 5 cm to 8 cm). Pulmonary sarcomatoid carcinomas with cavitation have also been reported [14]. The routes of metastasis are through the lymph nodes and/or blood [2,15-19]. The most common sites of metastasis are the same as for other NSCLCs (especially the brain, bone, adrenal gland, and liver). Yendamuri et al. reported that age, stage, and grade were correlated with overall survival [13]. Compared to non-sarcomatoid NSCLCs, pulmonary sarcomatoid carcinomas result in a substantially worse overall survival rate. Martin *et al*. enrolled 63 patients with pulmonary sarcomatoid carcinomas and 63 matched cases from 1133 NSCLC patients [11]. They found that the 5-year survival rate of pulmonary sarcomatoid carcinoma patients was 24.5% compared to 46.3% for NSCLC patients (p=0.01), with a median time to recurrence of 11.3 months and 61.4 months, respectively (p=0.001).

It has been hypothesized that the development of sarcomatoid areas occurs because of the coexistence of epithelial and mesenchymal malignant components, or of primary epithelial tumors with metaplasia [20]. Due to the similar molecular abnormalities in both components, the hypothesis of primary epithelial tumors with metaplasia is favored. Sarcomatoid areas are difficult to differentiate from real sarcomas using light microscopy, so IHC is diagnostically critical. Immunostaining of pan-cytokeratin, epithelial membrane antigen, and carcinoembryonic antigen provides useful markers of epithelial differentiation, particularly in small biopsy specimens. However, there may possibly be false negatives, and epithelial membrane antigens are not completely specific. Lewis *et al*. reported that p63, the epithelial cell adhesion molecule, and TTF-1 are other helpful immunohistochemical markers of sarcomatoid carcinomas [20]. In general, they are unencapsulated, tan-colored, and variegated with frequent hemorrhage and necrosis [3].

With regard to advanced pulmonary sarcomatoid carcinomas, nonsurgical modalities of treatment remain a challenge. Few studies on the genetic alterations that are used for targeted therapy exist. Pelosi *et al*. reported that pulmonary sarcomatoid carcinomas showed a nonrandom amplification of the anaplastic lymphoma kinase gene [21]. Kirsten rat sarcoma gene mutations can present a novel site for therapy with mitogen-activated protein kinase inhibitors [21]. A molecular analysis of 33 cases reported

that epidermal growth factor receptor tyrosine kinase domain inhibitors alone are not as effective as chemotherapy [22]. Therefore, early detection with a sufficient number of specimens for pathological diagnosis, followed by surgical resection, is the ideal scenario. Unlike previous studies demonstrating that pulmonary sarcomatoid carcinomas are located at the peripheral lung or chest wall, the current case presented as an endobronchial mass with pulmonary artery involvement, which might have been misdiagnosed as another type of NSCLC.

In conclusion, pulmonary sarcomatoid carcinoma is a rare form of NSCLC. It usually presents as a large, peripheral, and necrotic mass, and has a high risk of both local and distant recurrence, leading to a less favorable prognosis despite aggressive therapy.

References

1. Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. CA Cancer J Clin 2011; 61: 69.
2. Travis D, Brambillia E, Muller-Hermelink K, *et al*. WHO classification of tumours. Pathology and genetics of tumor of the lung, pleura, thymus and heart. Lyon: IARC press 2004; 53-8.
3. Travis WD. Sarcomatoid neoplasms of the lung and pleura. Arch Pathol Lab Med 2010; 134: 1645-8.
4. Girard N, Barbareschi M, Cordier JF, *et al*. What is a rare tumor, and how to deal with it clinically? Eur Respir Monogr 2007; 39: 85-133.
5. Fishback NF, Travis WD, Moran CA, *et al*. Pleomorphic (spindle/giant cell) carcinoma of the lung. A clinicopathologic correlation of 78 cases. Cancer 1994; 73: 2936-45.
6. Rossi G, Cavazza A, Sturm N, *et al*. Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements: A clinicopathologic and immunohistochemical study of 75 cases. Am J Surg Pathol 2003; 27: 311-24.
7. Ginsberg SS, Buzaid AC, Stern H, *et al*. Giant cell carcinoma of the lung. Cancer 1992; 70: 606-10.
8. Koss MN, Hochholzer L, Frommelt RA. Carcinosarcomas of the lung: A clinicopathologic study of 66 patients. Am J Surg Pathol 1999; 23: 1514-26.
9. Koss MN, Hochholzer L, O'Leary T. Pulmonary blastomas. Cancer 1991; 67(9): 2368-81.
10. Franks TJ, Galvin JR. Sarcomatoid carcinoma of the lung: Histologic criteria and common lesions in the differential diagnosis. Arch Pathol Lab Med 2010; 134: 49-54.
11. Martin LW, Correa AM, Ordonez NG, *et al*. Sarcomatoid carcinoma of the lung: A predictor of poor prognosis. Ann Thorac Surg 2007; 84: 973-81.
12. Pelosi G, Sonzogni A, De Pas T, *et al*. Pulmonary sarcomatoid carcinomas: a practical overview. Internat J Surg Pathol 2010; 18(2): 103-20.
13. Yendamuri S, Caty L, Pine M, *et al*. Outcomes of sarcomatoid carcinoma of the lung: a Surveillance, Epidemiology, and End Results Database analysis. Surgery 2012; 152: 397.
14. Chang YL, Lee YC, Shih JY, *et al*. Pulmonary pleomorphic (spindle) cell carcinoma: peculiar clinicopathologic manifestations different from ordinary non-small cell carcinoma. Lung Cancer 2001; 34: 91-7.
15. Davis MP, Eagan RR, Weiland LH, *et al*. Carcinosarcoma of the lung: Mayo Clinic experience and response to chemotherapy. Mayo Clin Proc 1984; 59: 598-603.
16. Berho M, Moran CA, Suster S. Malignant mixed epithelial/mesenchymal neoplasms of the lung. Semin Diagn Pathol 1995; 12: 123-39.
17. Mochizuki T, Ishii G, Nagai K, *et al*. Pleomorphic carcinoma of the lung: clinicopathologic characteristics of 70 cases. Am J Surg Pathol 2008; 32: 1727-35.
18. Stackhouse EM, Harrison EG Jr, Ellis FH Jr. Primary mixed malignancies of lung: carcinosarcoma and blastoma. J Thorac Cardiovasc Surg 1969; 57: 385-99.
19. Homma T, Doki Y, Tsuda M, *et al*. Uncontrollable midbrain hemorrhage due to brain metastasis of pulmonary pleomorphic carcinoma. Kyobu Geka 2008; 61: 335-9.
20. Lewis JS, Ritter JH, El-Mofty S. Alternative epithelial markers in sarcomatoid carcinomas of the head and neck, lung, and bladder-p63, MOC-31, and TTF-1. Modern Pathol 2005; 18: 1471-81.
21. Pelosi G, Gasparini P, Cavazza A, *et al*. Multiparametric molecular characterization of pulmonary sarcomatoid carcinoma reveals a nonrandom amplification of anaplastic lymphoma kinase (ALK) gene. Lung Cancer 2012; 77:

507-14.
22. Jiang XL, Liu YX, Chen C, *et al*. The value of biomarkers in patients with sarcomatoid carcinoma of the lung: molecular a nalysis of 33 cases. Clin Lung Cancer 2012; 13(4): 288-96.

肺類肉瘤上皮癌（梭狀細胞上皮癌亞型）以支氣管內腫塊和肺血管侵犯爲表現：罕見病例報告及文獻回顧

許家輔 *　蘇文彬 **　巫政霖 ***　林建中 *　曾堯麟 ****　張漢煜 *

肺類肉瘤上皮癌是一種罕見的非小細胞肺癌，約僅占所有肺癌的 0.1% 至 0.4%。病人常見於 60 至 70 歲的男性吸菸者，其臨床病程相當有侵犯性，且預後明顯比其餘的非小細胞肺癌來得差。肺類肉瘤上皮癌普遍生長為單一且體積大的腫瘤，常位於週邊且侵犯胸壁。儘管其行為如此惡性，但是很罕見到以支氣管內突出的腫瘤併肺血管侵犯為表現。在此，我們報告一位具有肺類肉瘤上皮癌（梭狀細胞上皮癌亞型）的非吸菸 59 歲女性案例，其腫瘤以支氣管內腫塊和肺血管侵犯為不尋常表現。*(胸腔醫學 **2014; 29: 238-245**)*

關鍵詞：梭狀細胞上皮癌，肺類肉瘤上皮癌

成功大學附設醫院　內科部　胸腔內科 *，內科部　腫瘤科 **，病理部 ***，外科部 ****
索取抽印本請聯絡：張漢煜醫師，成功大學附設醫院　內科部　胸腔內科，704 台南市北區勝利路 138 號

Seminal Vesicles Metastasis from Small Cell Lung Cancer: A Rare Entity

Wen-Chien Cheng*,***, Chih-Yen Tu*,**, Wei-Chih Liao*,***, Chia-Hung Chen*,***, Hung-Jen Chen*,***, Wu-Huei Hsu*,***

Seminal vesicle metastasis of a primary small cell lung cancer (SCLC) is rare. We present the case of a 59-year-old male who was diagnosed with SCLC of the left upper lung in January 2011 and was treated with chemotherapy and radiotherapy. He was later admitted for complaints of anal pain and dysuria during his regular follow-up. Abdominal computed tomography scan revealed an 8x5.5 cm mass in the left seminal vesicle. Histopathology after trans-rectal ultrasound-guided biopsy confirmed the diagnosis of SCLC. The patient then underwent concurrent chemo-radiotherapy (CCRT). His post-CCRT follow-up at 3 months showed complete response and no recurrence. The management of patients with lung cancer and dysuria should consist of a multi-disciplinary approach, and urologic organ metastasis should be included among the differential diagnoses. ***(Thorac Med 2014; 29: 246-251)***

Key words: lung cancer, small cell lung cancer, seminal vesicles metastasis

Introduction

Small cell lung cancer (SCLC) originates from neuro-endocrine bronchial cells [1]. It accounts for approximately 15-20% of all lung cancers throughout the world, with varying incidences in different countries [2]. SCLC is considered distinct from other lung cancers because of its clinical and biologic characteristics, which include aggressive behavior, rapid growth, and early spread to distant sites. Thus, its malignancy is the highest of all lung cancers. A simple 2-stage system developed by the Veterans Administration Lung Cancer Study Group, composed of limited-stage and extensive-stage disease, is now frequently used in clinical practice [3]. Chemotherapy is the cornerstone of treatment, but despite modest improvements in survival, outcome remains extremely poor.

SCLC is characterized by an initial sensitivity to chemotherapy and radiation, and early metastasis to regional lymph nodes and/or distant sites [4]. The common sites of distant metastasis are the brain, liver, adrenal glands, and bone [5]. Metastasis to the seminal vesicles

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; **Department of Respiratory Therapy, China Medical University, Taichung, Taiwan; ***School of Medicine, China Medical University
Address reprint requests to: Dr. Chih-Yen Tu, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, No. 2, Yude Road, Taichung, Taiwan

by different types of neoplasms, including lung cancer, is extremely rare, and prognosis is rather poor. This case report is of a patient with SCLC and left seminal vesicle metastasis who presented with dysuria and was successfully treated with concurrent chemo-radiotherapy (CCRT).

Case Report

A 59-year-old male was diagnosed with SCLC of the left upper lung, limited stage, in January 2011 after presenting with dyspnea on exertion (Figure 1). He underwent CCRT with radiotherapy and 6 cycles of chemotherapy using etoposide and cisplatin. His post-CCRT regular follow-up showed partial response without recurrence (Figure 2). Prophylactic cranial irradiation was then performed and completed in May 2011.

However, in February 2012, the patient was admitted to the emergency department for complaints of dysuria and anal pain of 2 days' duration. Digital examination revealed a mass lesion in the left prostate area. Abdominal computed tomography (CT) scan revealed an 8×5.5 cm

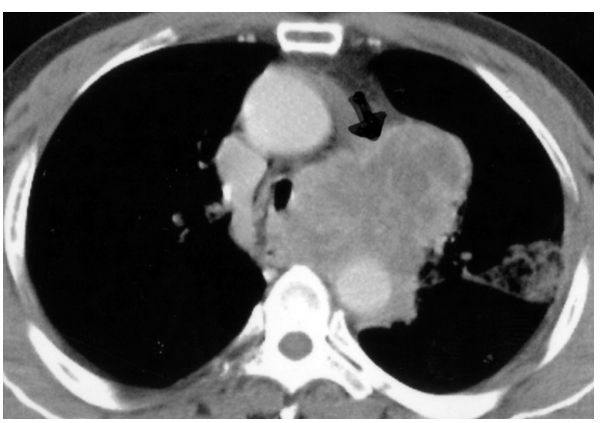


Fig. 1. Chest computed tomography imaging showing a left upper lung mass with mediastinal lymphadenopathy causing mild compression of the trachea (arrow).

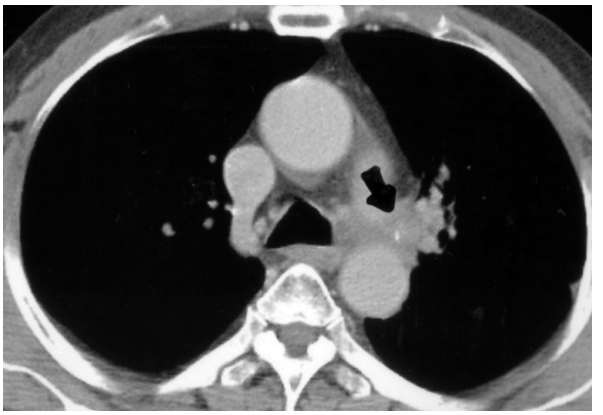


Fig. 2. Chest computed tomography imaging showing small cell lung cancer with partial response after concurrent chemo-radiotherapy (arrow).

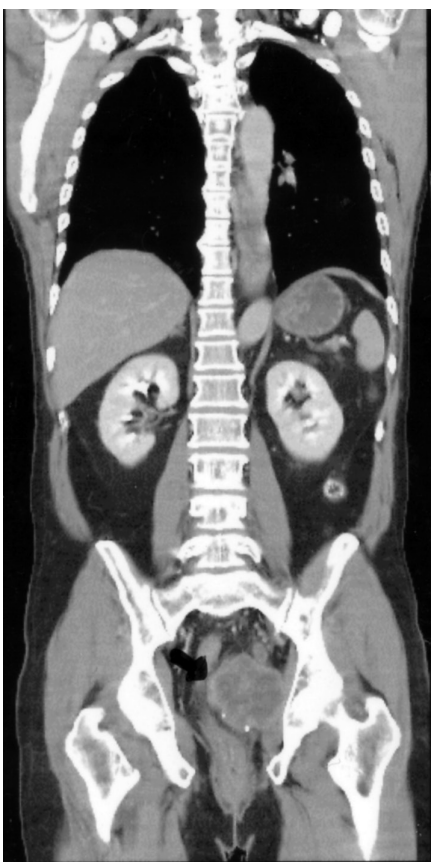


Fig. 3. Sagittal computed tomography imaging showing an 8x5.5 cm mass in the left seminal vesicle (arrow).

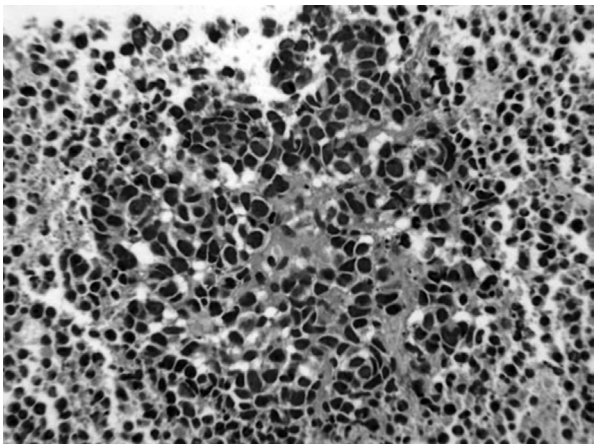


Fig. 4A. Nests of tumor cells with ovoid to spindle nuclei with scant cytoplasm.

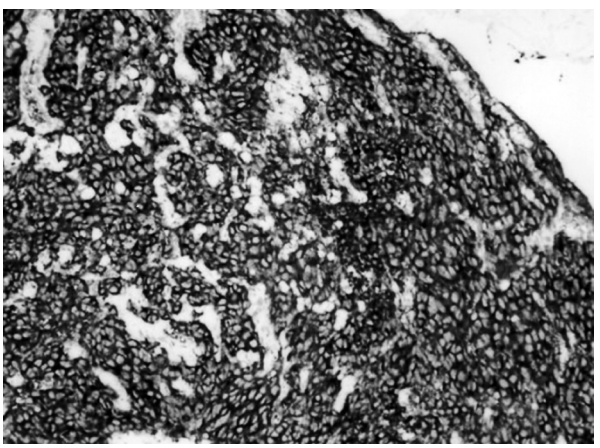


Fig. 4B. Immuno-histochemical staining revealed strong reactivity of synaptophysin on the lung carcinoma.

mass in the left seminal vesicle, complicated by left hydronephrosis and hydro-ureter due to obstruction of the left lower-third of the ureter by tumor compression (Figure 3). The tumor marker PSA was 0.439 ng/ml. Trans-rectal ultrasound-guided biopsy of the mass was performed and immuno-histochemical staining of the specimen revealed that it was reactive to TTF-1, synaptophysin, and CK (cytoplasmic stain), but negative for chromogranin A. The immuno-histochemical and pathologic features of the tumor indicated seminal vesicle metastasis of the SCLC (Figures 4A and 4B).

The patient underwent chemotherapy with etoposide and local radiotherapy to the seminal vesicle mass. There was almost complete response and his dysuria and hydronephrosis subsided.

Discussion

Malignancy is one of the most common causes of death, and many patients succumb to the complications of metastatic disease. Bronchogenic carcinoma is the leading cause of tumor-related deaths in developed countries. Common sites of metastasis from lung cancer include the brain, bone, adrenal glands, and liver. The seminal vesicle is an uncommon location for metastasis from lung cancer and very few such cases have been reported in the literature [6-7]. To date, there are only 2 case reports with seminal vesicle metastasis: 1 from hepatocellular carcinoma [6] and 1 from renal cell carcinoma [7]. A case of neuro-endocrine carcinoma of the seminal vesicles without lung lesions and presenting as Lambert Eaton syndrome also has been reported [8]. Despite the increasing number of cases of lung cancer, metastasis to the seminal vesicles is extremely rare.

In the current case report, the patient was admitted to the emergency department for dysuria. None of his symptoms reflected his previous SCLC. Primary seminal vesicle cancer was considered due to the stable condition of his SCLC. Distinguishing between the pathologic features of primary seminal vesicle malignancy and those of metastasis from lung cancer is necessary. The case presented was finally diagnosed as SCLC recurrence with seminal vesicle

metastasis, based on the immuno-histochemical and pathologic features of the tumor, and was successfully treated using the previous chemotherapy regimen of etoposide plus local radiotherapy. His seminal vesicle mass completely responded and his dysuria subsided.

Tumors of the seminal vesicles may be primary tumors or secondary tumors originating from adjacent organs like the bladder, prostate, or rectum. Primary seminal vesicle tumors are rare, and may be benign (i.e., papillary adenoma, cystadenoma, hydatid cyst, and amyloid deposition) or malignant (i.e., adenocarcinoma, sarcoma, cystosarcoma phyllodes, primary seminoma, and carcinoid). Adenocarcinoma is the most frequent malignant tumor [6]. The aim of treatment for primary seminal vesicle tumor is curative radical surgery prior to any infiltration of neighboring organs or even metastasis. Also, hormonal manipulation and radiotherapy seem to be effective as adjuvant treatment modalities [9].

Neuro-endocrine tumors represent approximately 20% of all primary lung neoplasms. Most lung neuro-endocrine carcinomas are SCLC. Although 95% of small cell carcinomas originate in the lung, they can also arise from extra-pulmonary sites such as the nasopharynx, gastro-intestinal tract, and genito-urinary tract [10-12]. Small-cell carcinoma of the seminal vesicle is rarely reported. To date, only 3 such cases have been reported [8,16-17]. Both pulmonary and extra-pulmonary small cell carcinomas have similar clinical and biologic behavior, leading to a high potential for widespread metastases [13].

In patients with limited-stage disease, response rates of 70-90% are expected after treatment with etoposide plus thoracic radiotherapy. In contrast, in extensive-stage disease, 60-70% response rates can be achieved with systemic chemotherapy alone [14]. Although SCLC has a relatively good initial response to chemotherapy and radiotherapy, relapse or disease progression may quickly occur, and 5-year survival is less than 2% [4]. The median survival rate is only 14-20 and 9-11 months for patients with limited and extensive-stage disease, respectively. After appropriate treatment, the 2-year survival rate is approximately 40% in patients with limited-stage disease, but less than 5% in those with extensive-stage disease [15].

In summary, seminal vesicle metastasis from lung cancer is extremely rare. To date, this is the first case report of a patient with SCLC presenting with seminal vesicle metastasis. Re-treatment with a CCRT regimen of etoposide plus radiotherapy leads to complete response.

References

1. Beasley MB, Brambilla E, Travis WD. The 2004 World Health Organization classification of lung tumors. Semin Roentgenol 2005; 40: 90-7.
2. Wahbah M, Boroumand N, Castro C, *et al*. Changing trends in the distribution of the histologic types of lung cancer: a review of 4,439 cases. Ann Diagn Pathol 2007; 11: 89-96.
3. Micke P, Faldum A, Metz T, *et al*. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer - what limits limited disease? Lung Cancer 2002; 37: 271-6.
4. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 2005; 366: 1385-96.
5. El Maalouf G, Rodier JM, Faivre S. Could we expect to improve survival in small cell lung cancer? Lung Cancer 2007; 57 (Suppl 2): 30-4.
6. Gong L, Zheng M, Li Y, *et al*. Seminal vesicles metastasis after partial hepatectomy for hepatocellular carcinoma. BMC Cancer 2011; 28: 111.
7. Matsuzaki K, Yasunaga Y, Fukuda S, *et al*. Seminal vesicle

metastasis of renal cell carcinoma. Urology 2009; 74: 1017-8.
8. Kreiner B, Denzinger S, Ganzer R, *et al*. Neuro-endocrine carcinoma of the seminal vesicles presenting with Lambert Eaton syndrome: a case report. J Med Case Reports 2010; 4: 320.
9. Thiel R, Effert P. Primary adenocarcinoma of the seminal vesicles. J Urol 2002; 168: 1891-6.
10. Brenner B, Tang LH, Klimstra DS, *et al*. Small-cell carcinomas of the gastro-intestinal tract: a review. J Clin Oncol 2004; 22: 2730-9.
11. Galanis E, Frytak S, Lloyd RV. Extra-pulmonary small cell carcinoma. Cancer 1997; 79: 1729-36.
12. Remick SC, Ruckdeschel JC. Extra-pulmonary and pulmonary small-cell carcinoma: tumor biology, therapy, and outcome. Med Pediatr Oncol 1992; 20: 89-99.
13. Johnson BE, Whang-Peng J, Naylor SL, *et al*. Retention of chromosome 3 in extra-pulmonary small cell cancer shown by molecular and cytogenetic studies. J Natl Cancer Inst 1989; 81: 1223-8.
14. Simon M, Argiris A, Murren JR, *et al*. Progress in the therapy of small cell lung cancer. Crit Rev Oncol Hematol 2004; 49: 119-33.
15. Chute JP, Chen T, Feigal E, *et al*. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. J Clin Oncol 1999; 17: 1794-801.
16. Hoppin EC, Rives RK. Small-cell carcinoma of the seminal vesicle responding to chemotherapy. Annals Oncol 1997; 8: 503-504.
17. Siracusano S, Bortolus R, Stener S. Primary small-cell carcinoma of the seminal vesicle treated by chemotherapy and radiotherapy BJU Internat 2001 88 (4cr), 442.

小細胞肺癌合併儲精囊轉移－病例報告

鄭文建 *,*** 涂智彥 *,** 廖偉志 *,*** 陳家弘 *,*** 陳鴻仁 *,*** 徐武輝 *,***

小細胞肺癌合併儲精囊轉移是少見的。我們報導一位五十九歲男性在 2011 年 1 月被診斷左上肺葉小細胞肺癌侷限型並且接受化學治療及放射線治療，在門診規則追蹤。此次來急診因為肛門疼痛及解尿疼痛。腹部電腦斷層發現在左側的儲精囊有一顆 8×5.5 公分的腫瘤。經直腸超音波指引切片病理報告呈現小細胞肺癌。此病人再次接受化學治療並放射線治療，在治療後三個月追蹤此病人左側儲精囊及症狀皆完全消除。在治療腫瘤病人有解尿疼痛的情況必須多方面去思考包含泌尿器官的轉移。*(胸腔醫學* ***2014; 29: 246-251)***

關鍵詞：肺癌，小細胞肺癌，儲精囊轉移

* 中國醫藥大學附設醫院　內科部　胸腔暨重症系，** 中國醫藥大學　呼吸治療學系，*** 中國醫藥大學　醫學系
索取抽印本請聯絡：涂智彥醫師，中國醫藥大學附設醫院　內科部　胸腔暨重症系，台中市北區育德路 2 號

Oseltamivir-Induced Delirium in an Elderly Patient: Report of a Case and Literature Review

Ching-Yuan Cheng, Jiunn-Song Jiang

Oseltamivir is an influenza virus neuraminidase inhibitor. It is commonly prescribed for the prevention and treatment of influenza virus infection. The most common side effects are gastrointestinal symptoms such as nausea, vomiting and abdominal pain. Delirium rarely has been reported in the elderly. We present the case of an 80-year-old man who developed delirium after taking oseltamivir. He had a past history of chronic obstructive pulmonary disease, type 2 diabetes mellitus, triple-vessel coronary artery disease that underwent coronary artery bypass graft surgery, hypertension, dyslipidemia, benign prostate hypertrophy and rheumatoid arthritis. He was admitted due to fever, dry cough and myalgia for 2 days. Influenza B rapid test was positive. Delirium developed 4 days after he took oseltamivir and gradually subsided after ceasing it. This case report should remind medical staff of possibility of inducing delirium in the elderly with oseltamivir use. ***(Thorac Med 2014; 29: 252-256)***

Key words: oseltamivir, influenza, delirium

Introduction

Oseltamivir is an influenza virus neuraminidase inhibitor. It is commonly prescribed for preventing and treating influenza virus infection. The most common side effects are gastrointestinal symptoms such as nausea, vomiting and abdominal pain [1-2]. Delirium has been rarely reported in the elderly [3-4]. We present the case of an 80-year-old man who developed delirium after taking oseltamivir.

Case Report

An 80-year-old man had the past history of chronic obstructive pulmonary disease, type 2 diabetes mellitus, triple-vessel coronary artery disease that underwent coronary artery bypass graft surgery, hypertension, dyslipidemia, benign prostate hypertrophy and rheumatoid arthritis. He complained of fever, cough, rhinorrhea, myalgia and poor appetite for 2 days. He was brought to the emergency department on 6 February 2012 due to cold sweating and a reduced blood sugar level (41 mg/dL by his own

Division of Chest Medicine, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Jiunn-Song Jiang, Division of Chest Medicine, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, No. 95, Wen Chang Road, Shih Lin District, Taipei, Taiwan

blood sugar meter). The influenza rapid test showed influenza B infection, and oseltamivir 75 mg BID PO was prescribed on the same day. Curam® (amoxycillin 1000 mg/clavulanic acid 200 mg) 1.2 g BID was also infused from 6 February 2012 to 12 February 2012 for concurrent bacterial pneumonia.

However, the patient suffered from confusion, agitation and incoherent speech on 9 February 2012. The blood test showed recovery from hypoglycemia. Brain CT found cortical brain atrophy without hemorrhage or tumor lesion. Lumbar puncture showed no infection signs, but EEG revealed frequent generalized asynchronous slow waves indicating metabolic or drug-induced encephalopathy. Under the impression of oseltamivir-induced delirium, he received an injection of haloperidol 2.5 mg IM, and oseltamivir was discontinued on the 4th day of oseltamivir use. The patient's delirium resolved 2 days later. The Naranjo scale (Table 1) [5] yielded a score of 7, which indicated a probable relationship between delirium and oseltamivir.

Discussion

In the post-marketing surveillance, oseltamivir-related neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) were reported primarily among pediatric patients. Neuropsychiatric adverse events (NPAEs) have been reported in some children taking oseltamivir in Japan since 2004-2005 [6]. These events include confusion, delirium, hallucinations, and self-injury. In 2006, the U.S. Food and Drug Administration added supplementary information to the package insert as follows: "People with the flu, particularly children, may be at an increase risk of

Table 1. Naranjo Scale

	Question	Yes	No	Don't know	score
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2	Did the adverse event appear after the suspected drug was given?	+2	-1	0	+2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
4	Did the adverse reaction appear when the drug was readministered?	+2	-1	0	0
5	Are there alternative causes that could have caused the reaction?	-1	+2	0	+2
6	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7	Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
				Total	7

Table 2. Patient Characteristics

Patient	Age/gender	Dose of oseltamivir	Onset of delirium	Management of delirium
1	83/male	75 mg QD	2 days	Haloperidol 0.5 mg bid for 2 days
2	62/male	75 mg BID	N/A	N/A
3	80/male	75 mg BID	4 days	Haloperidol 2.5 mg IM for 1 shot

N/A, not applicable

self-injury and confusion shortly after taking TAMIFLU and should be closely monitored for signs of unusual behavior". A study on abnormal behavior with oseltamivir use carried out in Japan showed the rate ratio of 1.57 for children with influenza taking oseltamivir to those who did not [7]. Another study reported 3051 NPAEs between 1999 and 2007: 2772 (90.9%) in Japan, 190 (6.2%) in the US and 89 (2.9%) in other countries. NPAEs were more common in children less than 16 years old. The NPAE generally occurred within 48 hours after taking oseltamivir for influenza [8]. The reason why NPAEs are more frequent in children remains unknown.

To our knowledge, oseltamivir-induced delirium in the elderly has been rarely reported. Three elderly patients that developed oseltamivir-related delirium have been reported (Table 2). The first was an 83-year-old man with a history of vascular dementia. He started taking oseltamivir 75 mg per day for flu-like symptoms. Agitation, aggression and increased confusion developed 2 days after starting the medication. He threw objects, tipped over tables and struck a nurse at the nursing home. He was then admitted to the psychiatric unit and oseltamivir was discontinued. Haloperidol 0.5 mg was prescribed twice daily, and the confusion resolved within 2 days [3]. Another reported patient was from Germany. He was a 62-year-old man with a history of coronary and hypertensive heart disease, type 2 diabetes mellitus and chronic renal insufficiency. He received oseltamivir for 4 days during the H1N1 outbreak in December 2009 for influenza with pneumonia. Delirium with psychotic and paranoid symptoms developed after the treatment [4].

Our patient developed delirium on the 4th day after receiving oseltamivir, and adverse effects improved 2 days after withdrawal. The time to onset of delirium ranged from 2 to 4 days in the elderly, unlike children, in whom it usually occurred within 2 days. Our patient was also elderly and had a number of comorbidities. The incidence of oseltamivir-induced delirium in the elderly is unknown. Rarely has there been local information in Taiwan reporting such an adverse reaction. Clinicians need to be aware of the possibility of inducing delirium with oseltamivir use in the elderly, especially those with comorbidities.

References

1. Bardsley-Elliot A, Noble S. Oseltamivir. Drugs 1999; 58: 851.
2. Treanor JJ, Hayden FG, Vrooman PS, *et al*. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA 2000; 283: 1016.
3. Kohen I. Oseltamivir-induced delirium in a geriatric patient. Int J Geriatr Psychiatry 2007; 22: 935-6.
4. Kruker AT, Krause M. Oseltamivir-induced delirium. Ther

Umsch 2010; 67: 613-5.
5. Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45.
6. US FDA. Meeting of the FDA Pediatric Advisory Committee, 16 November 2006. Available from URL: http://www.fda.gov/OHRMS/DOCKETS/ac/oc06.htm [Accessed July 3, 2008]
7. Yorifuji T, Suzuki E, Tsuda T. Oseltamivir and abnormal behaviors: true or not? Epidemiology 2009; 20: 619-21.
8. Toovey S, Prinssen EP, Rayner CR, *et al*. Post-marketing assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: an updated review. Adv Ther 2012; 29: 826-48.

Oseltamivir 引起之譫妄：病例報告以及文獻回顧

鄭景元　江俊松

Oseltamivir 為預防與治療流感病毒感染的神經胺酸酶抑制劑，此藥物最常見的副作用有噁心、嘔吐、腹痛等胃腸道症狀。老年人服藥後產生譫妄的副作用則少有文獻報導。我們提出了一個 80 歲的男性病例，此患者過去有慢性阻塞性肺病、第 2 型糖尿病以及冠狀動脈疾病經冠狀動脈繞道手術、高血壓、高血脂、攝護腺肥大以及類風濕性關節炎的病史。此次因為發燒、乾咳和肌肉痠痛兩天而前來求診，流感快篩結果顯示 B 型流感陽性。在服用 oseltamivir 治療第四天開始出現譫妄，症狀在停藥後逐漸消失。此案例報告提醒臨床醫療人員在老人使用 oseltamivir 應注意譫妄此副作用的發生。*(胸腔醫學 **2014; 29: 252-256**)*

關鍵詞：oseltamivir，流行性感冒，譫妄

新光吳火獅紀念醫院　內科部　胸腔內科
索取抽印本請聯絡：江俊松醫師，新光吳火獅紀念醫院　內科部　胸腔內科，台北市士林區 111 文昌路 95 號

Bronchopulmonary Sequestration with Increased FDG Uptake in PET-CT: A Case Report and Literature Review

Po-lan Su, Han-Yu Chang

Bronchopulmonary sequestration, also referred to as pulmonary sequestration, is a rare congenital malformation of the lower respiratory tract, in which a mass of non-functioning lung tissue is unable to communicate normally with the tracheobronchial tree. From a clinical standpoint, accurately diagnosing bronchopulmonary sequestration is crucial to the differential diagnosis of malignancies. PET-CT allows accurate differentiation between benign and malignant nodules. However, when bronchopulmonary sequestration is complicated by chronic infection from an organism such as Aspergillus, PET-CT will often detect a high FDG uptake, a symptom which may also indicate malignancy. Thus, choosing CT angiography rather than PET-CT can be critical to the accurate diagnosis of sequestration prior to pulmonary surgery. ***(Thorac Med 2014; 29: 257-262)***

Key words: bronchopulmonary sequestration, PET-CT

Introduction

Bronchopulmonary sequestration, also referred to as pulmonary sequestration, is a rare congenital malformation of the lower respiratory tract, in which a non-functioning mass of lung tissue is provided with systemic blood supply but lacks normal communication with the tracheobronchial tree [1]. Bronchopulmonary sequestration is subdivided into 2 categories based on the anatomical location: extra-lobar and intra-lobar [2]. Extra-lobar pulmonary sequestration is characterized by a mass which is separated from the lung. Most of this non-functioning tissue (63%) is located between the lower lobe and the diaphragm. However, cases of sub-diaphragmatic or retroperitoneal masses have also been reported (10~15%) [2-3]; 10% of cases were found to be asymptomatic. In contrast, intra-lobar sequestration involves a lesion that is located in normal lung tissue but shares the same visceral pleura as the parent lobe. Nearly all cases of intra-lobar sequestration are located in the lower lobe (98%) [2].

Patients suffering from extra-lobar sequestration are typically younger than those with intra-lobar sequestration. However, due to the insidious clinical course of bronchopulmonary

Division of Pulmonary Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
Address reprint requests to: Dr. Han-Yu Chang, Division of Pulmonary Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng-Li Rd. Tainan 704, Taiwan

sequestration, the age at diagnosis ranges from birth to 65 years [13]. The most common symptom of bronchopulmonary sequestration in late childhood or adolescence is recurrent pulmonary infection. In addition, bronchopulmonary sequestration often causes hemoptysis or chest pain in older patients [14] that mimics the clinical course of malignancy. Bronchopulmonary sequestration can also lead to other complications, including actual malignancy [15]. Prior to surgical intervention, differentiating between bronchopulmonary sequestration and malignancy can be difficult. This study presents a case in which bronchopulmonary sequestration mimicked the process of malignancy.

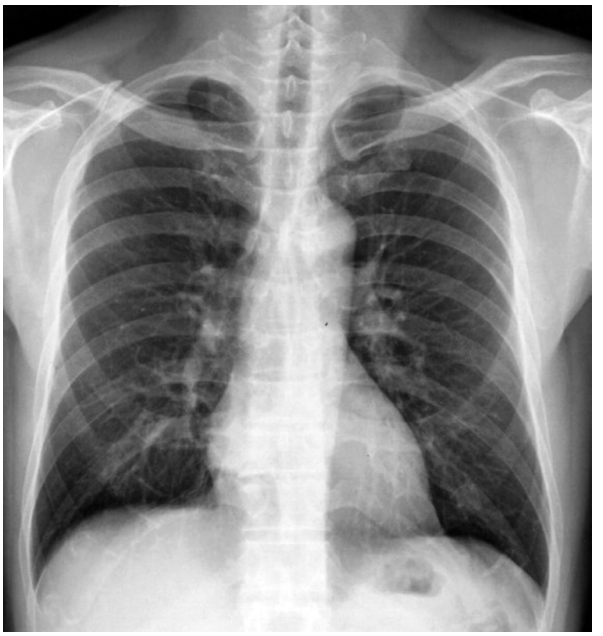


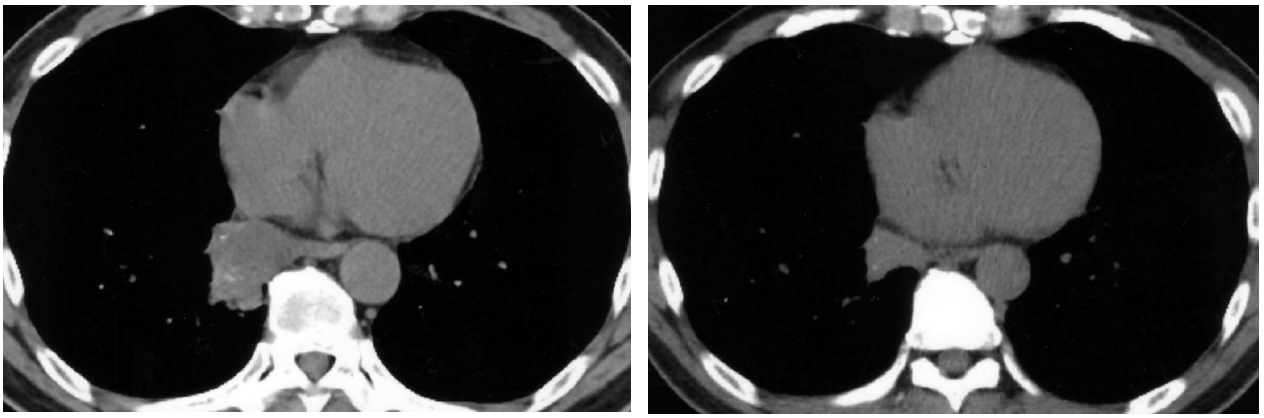
Fig. 1. Plain film showing increased density in the right retrocardiac region.

Case Report

A 56-year-old businessman with a history of heavy smoking checked in to the outpatient department due to chronic cough. Plain film results revealed increased density in the right retrocardiac region (Figure 1). Subsequent computed tomography (CT) of the chest revealed a lung mass (4×4.3×3.4 cm) with a cystic component and calcification (Figure 2A). This patient had undergone CT 4 years earlier, in which a mass lesion (2.7×2.9×3 cm) was found in same location (Figure 2B). A subsequent positron emission tomography (PET)-CT revealed a tumor with increased fluoro-deoxyglucose (FDG) uptake (3.0×2.5×1.0 cm, SUVmax: 3.4) in the lower lobe of the right lung. This was suspected to be chronic inflammation due to malignancy (Figure 3). CT angiography also revealed the mass was receiving systemic arterial supply from the aorta (Figure 4). A subsequent operation revealed chronic inflammation of the lung parenchyma and dilation bronchi and bronchioles. The lung alveoli showed focal emphysematous change as well as thick-walled vessels, indicating systemic vascular supply. These pathologic findings were compatible with bronchopulmonary sequestration.

Discussion

Bronchopulmonary sequestration can be diagnosed using prenatal ultrasound. Among adults, the diagnosis obtained from an image study is generally confirmed by pathologic examination. In a chest radiograph, intra-lobar sequestration may appear as an area of uniform opacity within the lung mass [4], a cystic lesion secondary to recurrent infection [4-5] or bronchial communication of the lesion, which is generally located in the lower lung field [6]. In contrast, extra-lobar sequestration may occur anywhere within the thoracic cavity and is far more difficult to detect using plain film. Thus, a CT scan is generally used to provide a more



(A) (B)

Fig. 2. CT image taken in 2012, showing a retrocardiac lung mass, 4×4.3×3.4 cm in size, with a cystic component and calcification in the axial section (A). CT image taken in 2008, showing a retrocardiac lung mass, 2.7×2.9×3 cm in size.

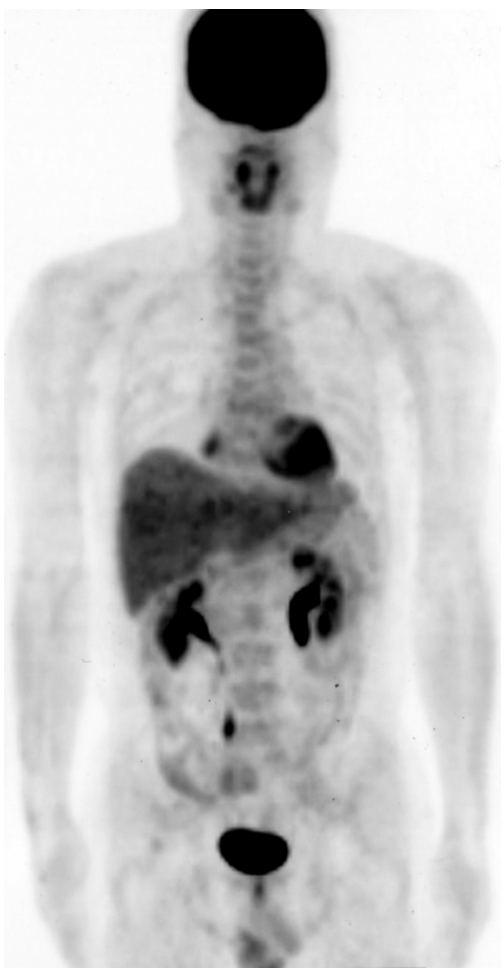


Fig. 3. PET-CT scan revealing a tumor with increased FDG uptake (3.0×2.5×1.0 cm, SUVmax: 3.4) in the lower lobe of the right lung.

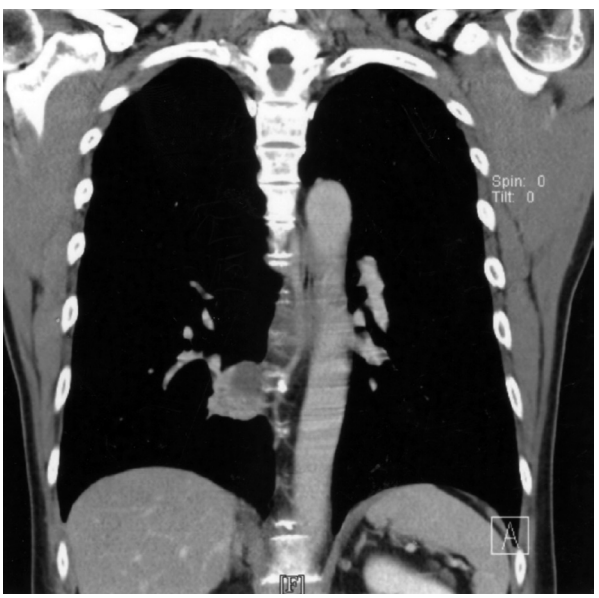


Fig. 4. Angiographic image showing systemic arterial supply from the aorta.

accurate diagnosis. This technique can reveal a number of features, including: (a) cysts containing air/fluid or soft-tissue masses, (b) emphysematous lung tissue surrounding cysts and/or soft-tissue nodules, and (c) lung hypervascularity [7]. Bronchopulmonary sequestration has been further defined as (a) a complex lesion

containing solid or fluid components combined with emphysematous lung tissue or (b) any basal lesion supplied by a systemic artery. CT angiography can be used to evaluate the arterial supply, venous drainage and parenchymal changes in a single examination. Thus, this technique is able to more accurately diagnose and preoperatively assess pulmonary sequestration [8].

Effective diagnosis of bronchopulmonary sequestration must accurately differentiate other cystic lesions within the thoracic cage, such as congenital pulmonary airway malformation (CPAM), diaphragmatic hernia, bronchogenic cysts, congenital lobar emphysema, and lung malignancy with cavitation. Other space-occupying chest lesions, such as mediastinal tumors, should also be considered. CPAMs are connected to the tracheobronchial tree, and are supplied mostly from pulmonary circulation. Any differential diagnosis involving intrathoracic cystic lesions could be based on CT or CT with angiography. In the case of this patient, neither current nor previous CT data showed evidence of tracheal-bronchial communication or hernia, and no other cystic lesions were noted in the lung parenchyma.

Differentiating between bronchopulmonary sequestration and malignancy can be challanging. The very slow growth of the lung mass in this patient made malignancy less likely. However, the possibility could not be totally excluded. The combined use of CT and FDG-PET can accurately differentiate between benign and malignant nodules. The sensitivity of FDG-PET has been reported to be as high as 97% and the specificity can reach 85%, with SUVmax >2 [9]. Another study reported high sensitivity (96%), specificity (83%) and positive predictive value (93%), with SUVmax >2.75 [16]. In the current case study, the patient presented hypermetabolic pulmonary lesions with SUVmax of 3.4; therefore, malignancy could not be ruled out. However, PET-CT may produce false-positive results in patients with complicating infections and inflammation. One report described the colonization of an intralobar sequestration by Aspergillus [10-11], which had the effect of mimicking malignancy when observed with PET/CT. In another study, PET imaging indicated increased blood flow and inflammation in the sequestrated segments. These observations were confirmed by surgical-pathological examination [12]. All of these cases developed in middle-aged individuals [11-12].

The current case illustrates the importance of considering sequestration in any diagnosis involving lesions in the posterior basal segment of the lower lobe of the lung. It should also be noted that pulmonary sequestration complicated with subclinical infection can appear as increased glycolytic activity in an FDG-PET study, thereby mimicking a malignancy. Thus, the choosing of CT angiography rather than PET-CT can be critical to the accurate diagnosis of sequestration prior to pulmonary surgery.

References

1. Landing BH, Dixon LG. Congenital malformations and genetic disorders of the respiratory tract (larynx, trachea, bronchi, and lungs). Am Rev Respir Dis 1979 Jul; 120(1): 151-85.
2. Corbett HJ, Humphrey GM. Pulmonary sequestration. Paediatr Respir Rev 2004 Mar; 5(1): 59-68.
3. Laje P, Martinez-Ferro M, Grisoni E, *et al*. Intraabdominal pulmonary sequestration. A case series and review of the literature. J Pediatr Surg 2006 Jul; 41(7): 1309-12.
4. Hernanz-Schulman M. Cysts and cyst-like lesions of the lung. Radiol Clin North Am 1993 May; 31(3): 631-49.
5. Hang JD, Guo QY, Chen CX, *et al*. Imaging approach to

the diagnosis of pulmonary sequestration. Acta Radiol 1996 Nov; 37(6): 883-8.
6. Ko SF, Ng SH, Lee TY, *et al*. Noninvasive imaging of bronchopulmonary sequestration. AJR Am J Roentgenol 2000 Oct; 175(4): 1005-12.
7. Ikezoe J, Murayama S, Godwin JD, *et al*. Bronchopulmonary sequestration: CT assessment. Radiology 1990 Aug; 176(2): 375-9.
8. Kang M, Khandelwal N, Ojili V, *et al*. Multidetector CT angiography in pulmonary sequestration. J Comput Assist Tomogr 2006 Nov-Dec; 30(6): 926-32.
9. Kim SK, Allen-Auerbach M, Goldin J, *et al*. Accuracy of PET/CT in characterization of solitary pulmonary lesions. J Nucl Med 2007 Feb; 48(2): 214-20.
10. Freixinet J, de Cos JD, Rodriguez de Castro F, *et al*. Colonisation with Aspergillus of an intralobar pulmonary sequestration. Thorax 1995 Jul; 50(7): 810-1.
11. Chan V, Boiselle PM, Karchmer AW, *et al*. Infected intralobar bronchopulmonary sequestration mimicking lung neoplasm on CT and positron emission tomography. Am J Roentgenol 2002 Sep; 179(3): 805.
12. Evman S, Batirel HF, Yüksel M. Late diagnosis of extralobar pulmonary sequestration: two cases with an uncommon malformation. Thorac Cardiovasc Surg 2012; 60(7): 485-7.
13. Conran RM, Stocker JT. Extralobar sequestration with frequently associated congenital cystic adenomatoid malformation, type 2: report of 50 cases. Pediatr Dev Pathol 1999 Sep-Oct; 2(5): 454-63.
14. Gezer S, Taştepe I, Sirmali M, *et al*. Pulmonary sequestration: a single-institutional series composed of 27 cases. J Thorac Cardiovasc Surg 2007 Apr; 133(4): 955-9.
15. Gatzinsky P, Olling S. A case of carcinoma in intralobar pulmonary sequestration. Thorac Cardiovasc Surg 1988 Oct; 36(5): 290-1.
16. Bar-Shalom R, Kagna O, Israel O, *et al*. Noninvasive diagnosis of solitary pulmonary lesions in cancer patients based on 2-fluoro-2-deoxy-D-glucose avidity on positron emission tomography/computed tomography. Cancer 2008 Dec 1; 113(11): 3213-21.

支氣管肺隔離症於正子攝影下呈現高度去氧葡萄糖攝取率：個案報告與文獻回顧

蘇柏嵐　張漢煜

支氣管肺隔離症，又稱作游離肺，是下呼吸道一種罕見的先天發育異常，通常是由無法正常通氣的肺泡組織組成。在臨床上要診斷游離肺最重要的步驟是與惡性腫瘤做區隔。一般而言，正子造影是目前最頻繁使用於惡性腫瘤診斷的工具。然而，當游離肺合併有慢性發炎感染如麴菌感染時，在正子造影下也會呈現類似惡性腫瘤的成像。因此，選用肺血管攝影觀察血管供應情形，是較好的術前診斷工具。*(胸腔醫學 **2014; 29: 257-262**)*

關鍵詞：支氣管肺隔離症，正子造影

成功大學附設醫院　內科部　胸腔內科
索取抽印本請聯絡：張漢煜醫師，成功大學附設醫院　內科部　胸腔內科，704 台南市北區勝利路 138 號