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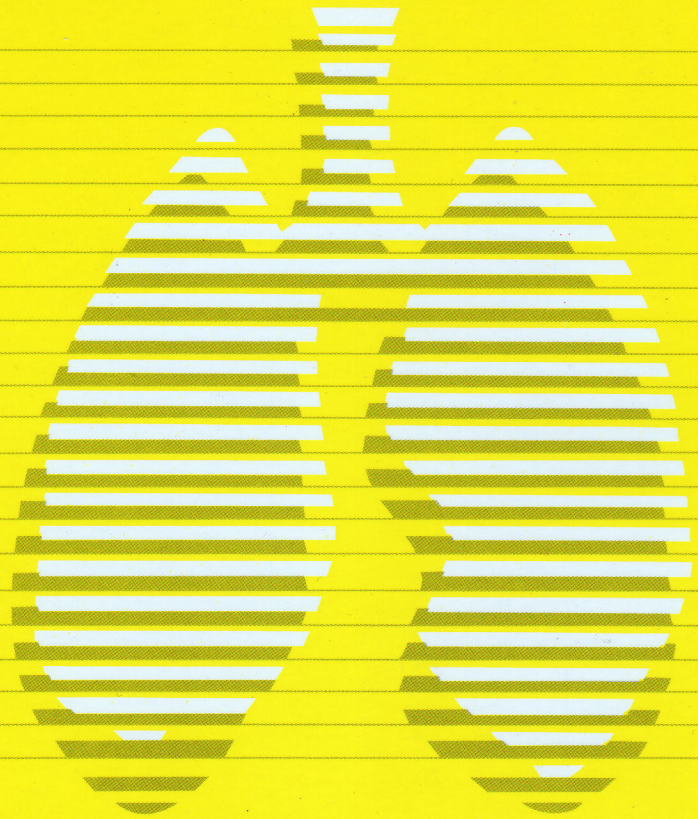

台灣胸腔暨重症加護醫學會

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原著

病例報告

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Orginial Articles

Case Reports

Validation Assessment of the Chinese Version of the International Restless Legs Scale

Yen-Lung Chen, Shih-Wei Lin*, Li-Pang Chuang*, Szu-Chia Lai**,
Rou-Shayn Chen**, Ning-Hung Chen*

Purpose: Diagnosis of restless legs syndrome (RLS) is difficult because the symptoms are non-specific and difficult for patients to describe clearly. Reports of RLS among Asians are rare and most studies in Asian populations showed a substantially lower prevalence than that in Caucasians. The reason for the low prevalence rate in Asian populations may be the difficulty of defining the symptoms in different languages. In order to provide a valid instrument for the Chinese-speaking population, the original International Restless Legs Scale (IRLS) was translated into Chinese and then validated in this study.

Methods: Nineteen bilingual patients were requested to answer the English-language version of the IRLS and then the Chinese version 2 weeks later. The other 37 patients were requested to answer the Chinese version of the IRLS (IRLS-C) twice at a 2-week interval. All patients were rated for severity of RLS using the IRLS, and a clinical global impression (CGI) of the severity was determined before and after standard treatment.

Results: The correlation coefficient between the IRLS-C and the original IRLS was 0.745 (p<0.0001). The retest ICC reliability for the IRLS-C total score was 0.712, and the Cronbach's α coefficient value was 0.84. The correlations between the IRLS-C and the CGI were significant (r=0.430, p=0.005).

Conclusions: The ILRS-C is a valid, reliable, and sensitive measure that can be used to evaluate the severity of RLS among Chinese-speaking adults. ***(Thorac Med 2013; 28: 65-72)***

Key words: restless legs syndrome, International Restless Legs Scale, Chinese version, validation

Introduction

Restless legs syndrome (RLS) is a common sensorimotor disorder first described by Willis in 1672. This syndrome is characterized by an urge to move, is associated with paresthesias, worsens in the evening and is relieved by activity. However, the symptoms of RLS are non-specific and sometimes difficult for patients to describe clearly, thus making the diagnosis of RLS difficult and leading to a varying prevalence rate among reports. RLS has affected as

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much as 15% of the adult general population in previous reports [1-2]. Some studies have suggested that the prevalence was higher in women than in men and it significantly increased with age [3-5]. However, reports on RLS prevalence in Asians are rare and the results are highly variable. Most studies of Asian populations showed a substantially lower prevalence (0.1% to 4%) than among Caucasians [6-9], and the reason for this is not clear. Difficulty defining the symptoms based on the definitions in different languages is a possible reason. To more easily recognize this disease, it is important to have an adequate tool for the diagnosis and evaluation. In order to provide a valid instrument, the International RLS Study Group (IRLSSG) developed a rating scale for measuring the severity of RLS (the International Restless Legs Scale or IRLS) in 1995 [10]. The modified version was published in 2003 [11]. This rating scale is now well accepted by researchers of RLS all over the world. The aims of this study were to translate the original IRLS into Chinese and to validate the translated version.

Patients and Methods

Patient population

Patients presenting to sleep clinics with the chief complaints of difficulty initiating sleep, dreamy and shallow sleep or sleep fragmentation were evaluated. A total of 137 patients who met the 4 criteria of RLS: an urge to move, an association with paresthesias, worsening in the evening and relieved by activity, were invited to enter the study. Diagnoses of RLS were made according to IRLSSG criteria [10] Patients were not excluded if they had 'secondary' forms of RLS, i.e., RLS associated with peripheral neuropathy, radiculopathy, or renal function impairment. Participants were excluded if they had a history of neuroleptic exposure, neuroleptic-induced akathisia, or any other condition that could be confused with RLS. Those subjects who took any medications known to affect the severity of RLS symptoms were also excluded. Pregnant patients were excluded from the treatment. Bilingual patients were requested to answer the English version of the IRLS and then the Chinese version 2 weeks later. Thirty-seven patients were requested to answer the Chinese version of the IRLS (IRLS-C) twice at a 2-week interval. The severity of RLS was evaluated in all patients using the IRLS, and the clinical global impression (CGI) of the severity was evaluated by the clinicians before treatment. Standard treatment, such as a dopaminergic agent, was prescribed. The patients were asked to complete the IRLS-C again, and the CGI was re-evaluated 1 month later. The protocols were approved by the Institutional Review Board of Chang Gung Memorial Hospital. All participants provided written informed consent.

International Restless Legs Scale (IRLS)

The rating scale was developed on the basis of questions proposed by members of the IRLSSG. The final version of the scale includes 10 questions. Each question has a set of 5 response options graded from no RLS or impact (score=0) to very severe RLS or impact (score=4). This produces a total score that could range from 0 to 40 (Table 1). The user agreement for the IRLS and the authorization to translate the IRLS were obtained from Mapi Research Trust.

Instrument translation

Development of the IRLS-C followed the standard forward step, backward step, and pre-

Table 1. The ten questions on the International Restless Legs Scale

1. Overall, how would you rate the RLS discomfort in your legs or arms?
2. Overall, how would you rate the need to move around because of your RLS symptoms?
3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?
4. Overall, how severe is your sleep disturbance from your RLS symptoms?
5. How severe is your tiredness or sleepiness from your RLS symptoms?
6. Overall, how severe is your RLS as a whole?
7. How often do you get RLS symptoms?
8. When you have RLS symptoms, how severe are they on an average day?
9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work life?
10. How severe is your mood disturbance from your RLS symptoms – for example angry, depressed, sad, anxious or irritable?

test step for instrument translation (Table 2). The pretest step was performed using a bilingual lay panel consisting of 3 heterogeneous individuals to measure comprehensibility, test translation alternatives, highlight unexpected errors, and reveal inappropriate items. A separate panel consisting of 19 bilingual testees was asked to answer both the IRLS and the IRLS-C at a 2-week interval. Spearman's rank order correlation coefficient was used to calculate the correlation between the IRLS-C and the original IRLS.

Reliability of the IRLS-C

Spearman rank order correlation coefficients were used to assess the item-total correlations for the IRLS-C. Cronbach's α correlation coefficients were used as the measure of internal consistency. Thirty-seven out of 137 participants without a known interval clinical change in their sleep complaints were retested with the IRLS-C at a 2-week interval. Intra-class correlations (ICC), as well as Spearman rank order correlation coefficients, were used to assess the test-retest reliability for individual items and for total survey.

Validity of the IRLS-C

The IRLS-C was assessed for convergent validity through correlations to the CGI. Spearman rank order correlation coefficients of the changes in the IRLS-C and the CGI were reported.

Responsiveness of the IRLS-C

Patients that underwent the validity test were again assessed with the IRLS-C 1 month after a stable dosage of RLS medications. Longitudinal sensitivity to clinical change was calculated as the standardized response mean (SRM = response mean/response standard deviation).

Results

Study population

Mean age of the enrolled participants was 47.3 ± 13.5 years (range 22-91) and males accounted for 51.8% of the study population. The mean body mass index (BMI) was 26.7 ± 5.7 (range 17.5-42.3).

Table 2. Chinese version of the International Restless Legs Scale

請您回答以下十個問題，此問卷調查是用來測量您夜間肢體不寧症之嚴重程度

在過去的一星期中，

	0	1	2	3	4
整體上，您認為因夜間肢體不寧症引起手臂或腳不舒服感覺的嚴重度為何？	一點都沒有	輕微	中等	嚴重	非常嚴重
整體上，您認為因夜間肢體不寧症使您需要起來活動的嚴重度為何？	一點都沒有	輕微	中等	嚴重	非常嚴重
整體上，您活動之後會減輕夜間肢體不寧症所造成手臂或腳不舒服的嚴重度為何？	沒有症狀，所以這個問題不適用	完全減輕或幾乎完全減輕	中等減輕	輕微減輕	完全沒減輕
整體上，您的睡眠品質受到夜間肢體不寧症症狀影響有多嚴重？	一點都沒有	輕微	中等	嚴重	非常嚴重
整體上，您因為夜間肢體不寧症症狀，造成白天的疲勞感或昏睡感有多嚴重？	一點都沒有	輕微	中等	嚴重	非常嚴重
整體來看，您的夜間肢體不寧症有多嚴重？	一點都沒有	輕微	中等	嚴重	非常嚴重
您的夜間肢體不寧症的症狀有多常發生？	一點都沒有	偶爾發生(這是指一星期一天或更少)	有時候發生(這是指一星期二到三天)	經常發生(這是指一星期四到五天)	常常發生(這是指一星期六到七天)
當您有夜間肢體不寧症症狀時，這些症狀平均有多嚴重？	一點都沒有	輕微(這是指一天一小時或更少)	中等(這是指一天一到三小時)	嚴重(這是指一天三到八小時)	非常嚴重(這是指一天八小時或更多)
整體上，您的夜間肢體不寧症症狀干擾您每天日常生活的情況有多嚴重？例如：進行令人滿意的家庭生活、社交、學校或工作。	一點都沒有	輕微	中等	嚴重	非常嚴重
您的夜間肢體不寧症症狀影響到您的心情有多嚴重？例如：生氣、憂鬱、悲傷、焦慮、煩躁。	一點都沒有	輕微	中等	嚴重	非常嚴重

本中文版IRLS為Mapi Research Trust正式授權Dr. Chen, Ning-Hung (email:ninghung@yahoo.com.tw) 翻譯及使用

Correlation between the IRLS-C and the original IRLS

The correlation coefficient of the IRLS-C and the original IRLS obtained from 19 bilingual testees was 0.745 (p<0.0001), indicating excellent linguistic interchangeability between the 2 scales.

Reliability of the IRLS-C

The retest ICC reliability for the IRLS-C total score was 0.712. The ICCs for individual IRLS-C items were shown in Table 3. Spearman correlation coefficients for the individual items and total score were shown in Table 4. The test-retest reliability of the IRLS-C was comparable

to that of the original IRLS with correlation coefficients varying from 0.400 to 0.741.

The internal consistency of the Chinese version of the IRLS was assessed using the Cronbach's α correlation coefficient and by computing item-total correlations. The Cronbach's α coefficient value was 0.84 for the IRLS-C total, and this met the criterion for a reliable measure (>0.7) for population studies. Item-total intra-survey reliability coefficients varied from 0.624 (item 5) to 0.928 (item 6) (Table 5).

Table 3. The retest ICC reliability of the Chinese version of the International Restless Legs Scale (n=37)

Individual item	ICC reliability	*p*
1	0.603	<0.001
2	0.479	0.007
3	0.553	<0.001
4	0.543	<0.001
5	0.721	<0.001
6	0.628	<0.001
7	0.672	<0.001
8	0.497	0.001
9	0.361	0.014
10	0.463	0.002
Total score	0.712	<0.001

Table 4. Test-retest reliability of the Chinese version of the International Restless Legs Scale (n=37)

Individual item	Spearman rank order correlation coefficient (*r*)	*p*
1	0.652	<0.001
2	0.505	0.007
3	0.477	<0.001
4	0.580	<0.001
5	0.741	<0.001
6	0.639	<0.001
7	0.690	<0.001
8	0.544	0.001
9	0.400	0.014
10	0.486	0.002
Total score	0.729	<0.001

Table 5. The internal consistency of the Chinese version of the International Restless Legs Scale

Individual item	Item-total reliability	
	Chinese IRLSQ, N=37	
1	0.904	<0.001
2	0.828	<0.001
3	0.637	<0.001
4	0.887	<0.001
5	0.624	<0.001
6	0.928	<0.001
7	0.736	<0.001
8	0.733	<0.001
9	0.662	<0.001
10	0.793	<0.001

Validity of the IRLS-C

The correlations between the IRLS-C and the CGI were significant (r=0.430, p=0.005).

Responsiveness of the IRLS-C

The IRLS-C was 20.41 ± 10.83 before treatment for 27 patients who underwent medical therapy, and was 14.67 ± 7.84 1 month after treatment. This change (-5.74 ± 11.29) was significant (p=0.014). The standardized response mean for the IRLS-C was -0.508.

Discussion

RLS is characterized by the sensation of an urge to move the legs that worsens at rest and is temporarily relieved by movement. It becomes worse in the evening and during the night and is frequently associated with paresthesias [10,12-

13]. It occurs with sleep disturbance frequently and is associated with periodic limb movements. Patients with RLS might not seek help and may be misdiagnosed due to the difficulty in clearly describing their symptoms. RLS can be confused with muscle cramping, insomnia or neuropathy if physicians are not aware of the characteristics and diagnostic criteria for RLS. The high prevalence establishes RLS as 1 of the most common movement disorders. The etiology of the reported lower prevalence of RLS in Asian populations includes racial differences, primary physicians lacking awareness of RLS, and the language problem [3-5,7,14-17]. The language barrier, especially when translating the diagnostic criteria into another language, could be a possible reason for the under-diagnosis of this syndrome. In this study, we introduced the IRLS-C as a valid and reliable disease-specific health measure that can be used to evaluate Chinese-speaking adult patients. The model approach to translation was used in this study in order to establish a basis for cross-national comparisons to the original validation of the IRLS [18].

The correlation between the IRLS-C and the original IRLS was as high as 0.745, indicating good linguistic and conceptual interchangeability between the Chinese and English versions. An ICC of less than 0.4 usually indicates poor reproducibility, while an ICC larger than 0.75 may indicate excellent reproducibility. Generally speaking, the IRLS-C demonstrated robust test-retest reliability for individual items and for total score, except item 9. Our retest reliability findings were similar using both ICC and Spearman correlation coefficients. Compared to the other items, the low correlation coefficient of 0.4 for item 9 could probably be ascribed to the fact that most of our patients visited the sleep clinic for nighttime symptoms, and did not consider daytime symptoms to be related to RLS. The Cronbach's α value of the IRLS-C (0.84) met the criteria for a reliable survey (0.7).

According to the established criteria, a SRM of more than 0.8 usually indicates excellent responsiveness [19]. The SRM for the IRLS-C was fair (0.508), based on this standard. The limitation in using the SRM as a measure of responsiveness should be noted. Nevertheless, the IRLS-C proved to be able to capture this clinical change.

The validation assessment demonstrated only a minor language effect and the performance characteristics of the IRLS-C were compatible with the English version of the IRLS. We conclude that the ILRS-C is a valid, reliable, and sensitive measure that can be used to evaluate the disease severity of RLS for millions of Chinese-speaking adults.

Acknowledgements

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中文版國際不寧腿症候群量表之效度分析

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前言：不寧腿症候群（Restless Legs Syndrome）由於症狀不具專一性，且病患常無法清楚描述其症狀，故在臨床上診斷不易。目前對於亞洲地區不寧腿症候群的研究仍不多，其中大部分研究顯示亞洲地區之不寧腿症候群盛行率遠低於高加索人種。亞洲地區不寧腿症候群盛行率偏低的原因可能來自於言語的表異造成症狀難以清楚定義。本研究將對 International Restless Legs Scale（IRLS）量表進行中文翻譯，並進行信度及效度檢驗，以提供中文使用族群臨床評估使用。

方法：有 19 名熟悉中文及英文的受試者進行中文版及英文版 IRLS 量表之相關性分析，受試者先進行英文版量表之填寫，並於兩週後進行中文版量表填寫。另有 37 名受試者進行中文版 IRLS 量表信度分析，受試者進行兩次中文版量表之填寫，期間間隔兩週。隨後所有的病患都會給予不寧腿症候群的治療，治療前後同時以中文版 IRLS 量表及臨床整體印象評估表（Clinical Global Impression, CGI）進行不寧腿症候群的嚴重度評估。

結果：中文版及英文版 IRLS 量表之間的相關係數（correlation coefficient）為 0.745（p<0.0001），中文版 IRLS 量表的再測組內相關係數（retest ICC reliability）為 0.712，Cronbach's α coefficient 值為 0.84。中文版 IRLS 量表和 CGI 之相關性分析具有意義（r=0.430, p=0.005）。

結論：中文版 IRLS 量表為一項具有信度、效度及敏感度之評估工具，可適用在中文使用族群中進行不寧腿症候群之嚴重度評估。*(胸腔醫學* ***2013; 28: 65-72)***

關鍵詞：不寧腿症候群，國際不寧腿症候群量表，中文版，效度

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索取抽印本請聯絡：陳濬宏醫師，長庚紀念醫院暨長庚大學　呼吸胸腔科系及睡眠中心，桃園縣龜山鄉頂湖路 123 號

Continuous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment May Not Hinder the Survival of Patients with Primary Lung Adenocarcinoma despite Indolent New Lesions

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Background: Lung adenocarcinoma treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) eventually develops progressive disease (PD) due to acquired resistance. However, since there are few published reports on the survival benefit of continuous EGFR-TKI administration for indolent new lesions, the present study retrospectively analyzed the possible treatment effect on PD status as defined by the Response Evaluation Criteria in Solid Tumors (RECIST).

Methods: From January 2005 to November 2009, the data of 37 lung adenocarcinoma patients were prospectively recorded and retrospectively analyzed and evaluated. All patients had at least 6 months of progression-free survival (PFS) with EGFR-TKI and definite new lesions during EGFR-TKI therapy, with the primary targeted lung lesions remaining regressive or stable. Twenty-six patients continued and 11 discontinued EGFR-TKI therapy. Overall survival (OS), survival after discontinuation of EGFR-TKI, and survival after the appearance of definite new lesions were compared.

Results: The median OS was 480 days for the discontinuation group and 771.5 days for the continuation group (p=0.1838). Median survival time after discontinuation of EGFR-TKI was 117.0 days and 143.0 days in the 2 groups, respectively (p=0.9106), while median survival time after the appearance of indolent new lesions was 152.0 days and 262.0 days, respectively (p=0.0571).

Conclusion: Continuous EGFR-TKI administration in patients with primary lung adenocarcinoma with an initial response and the appearance of new indolent lesions may not hinder the survival benefit. ***(Thorac Med 2013; 28: 73-88)***

Key words: epidermal growth factor receptor tyrosine kinase inhibitors, new lesions, progressive disease, overall survival, progression-free survival

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Introduction

Lung cancer is the most common cancer and leading cause of cancer-related deaths worldwide [1]. Approximately 85% of primary lung cancers are non-small cell lung cancer (NSCLC), and adenocarcinoma accounts for approximately 40% of lung cancers [2]. For non-resectable lung cancers (~80% of NSCLC), the prognosis is poor, with mean survival of 8-14 months [3]. Aside from chemotherapy, anti-epidermal growth factor receptor (EGFR) agents have been developed as treatment for NSCLC [4]. Although a subset of patients with favorable EGFR mutations benefit from EGFR targeted therapy [5-6], most patients eventually develop progressive disease (PD) due to acquired resistance, which may be related to a 2nd-site EGFR mutation or MET amplification, or others [7].

The clinical definition of acquired resistance is not clear and previous reports have revealed that progression of local lesions may not represent systemic resistance [8-12]. In clinical practice, lung adenocarcinoma patients on EGFR-TKI with progression-free survival (PFS) of more than 6 months develop indolent new lesions but remain clinically stable when EGFR-TKI is continued. New lesions are considered when a lesion is identified on follow-up imaging in an anatomic location without lesions at baseline [13]. The appearance of 1 or more new lesions is defined as PD by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.0, published in 2000) [14].

However, according to the revised RECIST 1.1 guidelines (2009), the first appearance of new lesions may not definitively indicate PD. If new lesions cannot be identified initially, treatment may be continued until the next scheduled assessment. Nonetheless, follow-up imaging that confirms new lesions should also confirm PD [13]. Therapeutic agents should then be altered. Acute deterioration after EGFR-TKI withdrawal has been reported in EGFR-mutant lung cancer with acquired resistance [10], but in clinical practice, some patients with a first appearance of new malignant lesions and PD regain disease stability when the original EGFR-TKI treatment is continued.

Thus, RECIST 1.1-defined PD for new malignant lesions may not indicate the need to change EGFR-TKI. This study aimed to determine if survival of the subset group with controlled targeted lesions and new local malignant lesions could be affected by discontinuing EGFR-TKI. Previous studies without EGFR mutation analysis suggested that lung adenocarcinoma had a more favorable response to EGFR-TKI than other types of NSCLC [15-17], but EGFR mutation analysis in clinical practice was not available in the study institute before 2009. Thus, lung adenocarcinoma was selected for survival analysis in the present study to avoid biological confounding factors from other NSCLC sub-types.

Methods

Patient selection

From January 2005 to November 2009, 436 patients diagnosed with stage III or IV primary lung adenocarcinoma who underwent 1st-, 2nd-, or 3rd-line targeted therapy with gefinitib or erlotinib at Chang-Gung Memorial Hospital (CGMH), a university-affiliated hospital in Taiwan, were screened. All were enrolled in the National Health Insurance Program of Taiwan and received comprehensive and updated therapy for NSCLC. The patients were evaluated to

determine the disease stage before the start of treatment, at regular intervals and for disease progression or relapse. The disease stage was determined by complete medical history, physical examination, imaging surveys including chest X-ray (CXR) and computed tomography (CT) of the chest and abdomen, and additional staging procedures like magnetic resonance imaging (MRI) of the head, bone scintigraphy, and fluorodeoxyglucose positron-emission tomography (FDG-PET). Tumor response was assessed based on RECIST 1.0 at the time of therapy and re-evaluated using RECIST 1.1 during the study.

Clinical information was prospectively recorded following the CGMH Lung Cancer Protocol and retrieved from the Cancer Registry System of the Cancer Center of CGMH. The hospital's institutional review board approved the study (CGMH IRB No. 100-3723B).

From the prospective recording and registry system, 37 patients with a mean age of 60.8 ± 11.8 years, PFS of at least 6 months under EGFR-TKI treatment, and the appearance of new lesions with controlled primary targeted lung lesions but without related clinical manifestations were enrolled. The retrospectively analyzed data included demographics (age, gender), initial lung cancer stage, performance status (PS), smoking status, line of EGFR-TKI and duration, PFS, overall survival (OS), survival after discontinuation of EGFR-TKI, survival after the occurrence of new lesions, and site of the new lesions. There were no EGFR mutation tests during the study due its retrospective nature and because the tests were not routinely used in the study hospital before 2009.

Treatment after the appearance of indolent new lesions

Of the 37 patients, 26 continued and 11 discontinued EGFR-TKI therapy after the appearance of new lesions. OS, survival after discontinuation of EGFR-TKI, and survival after the definite appearance of new lesions were compared between these 2 groups. All received very close follow-up with CXR every 1-4 weeks and CT every 1-2 months to detect pulmonary masses or other new lesions, and MRI for bone or brain lesions, so as to evaluate treatment response. The pulmonary oncologists integrated information from radiographic images, as well as the speed of progression during the interval between imaging studies, and the performance status for decision-making regarding therapy after re-staging. EGFR-TKI was used in the continuation group until PD of the primary targeted lung, persistent progression of new lesions, or deterioration of related symptoms.

Statistical analysis

Data are presented as mean ± standard deviation, except where otherwise mentioned. Since the data did not approximate a Gaussian distribution, non-parametric statistical analysis, the Mann-Whitney U test, was performed for unpaired data to assess the significance of difference between 2 groups. Frequency distributions between the 2 groups were tested using chi-square or Fisher's exact probability tests. Survival rates were calculated using the Kaplan-Meier method, and comparison of survival curves was based on the log rank test. All p values were 2-sided and $p<0.05$ was considered statistically significant. GraphPad Prism (version 5.0; GraphPad Software, San Diego, CA) was used for all statistical analyses.

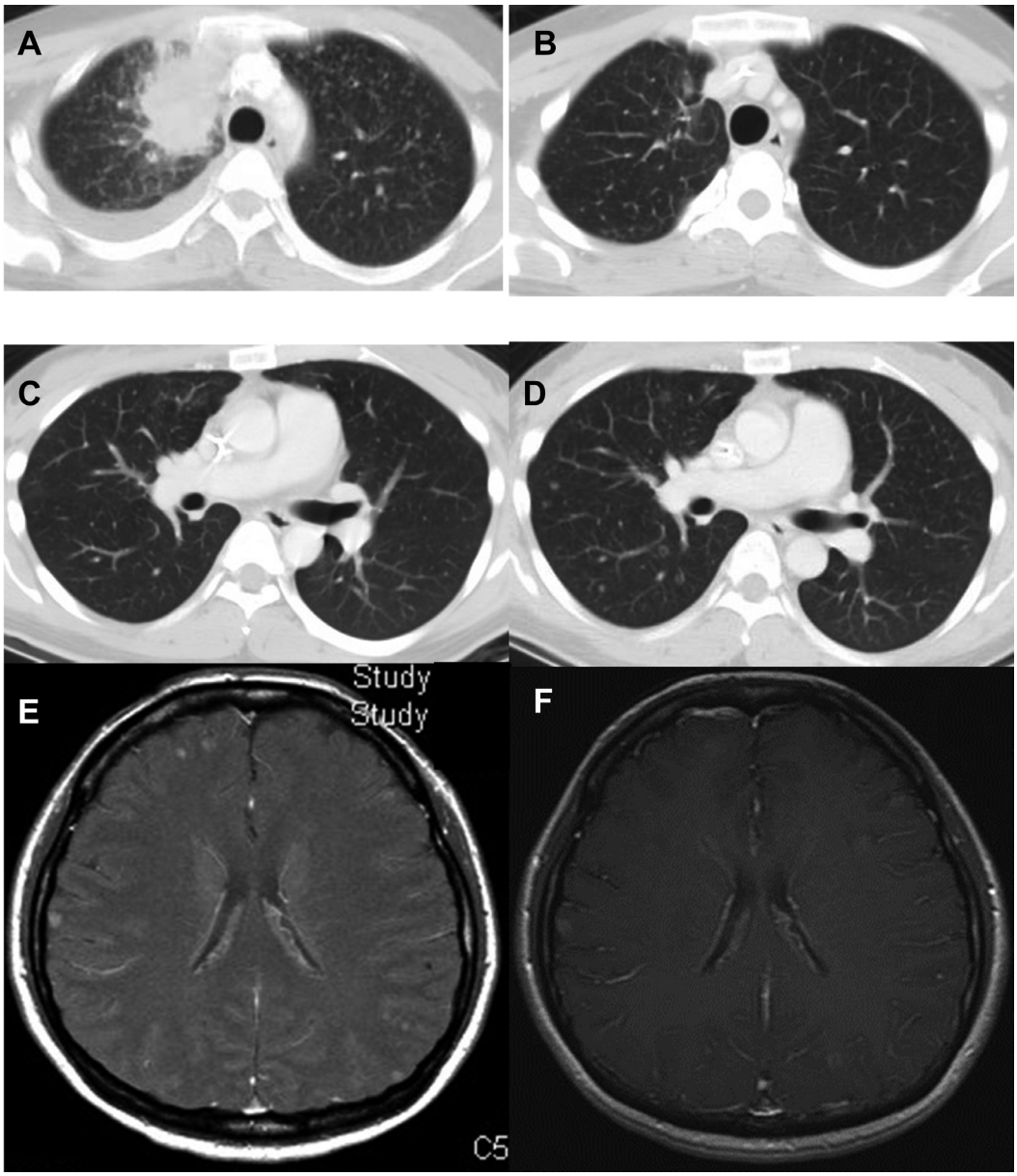

Fig. 1. A patient with primary lung adenocarcinoma on gefitinib with definite new lung and brain lesions. Stationary primary lung lesion with new lung and brain lesions on gefitinib treatment. (A) Primary right upper lung tumor before 2nd line gefitinib treatment. (B) Primary right upper lung tumor showed regression after 207 days of gefitinib treatment. (C) First appearance of new, minute, nodular lung lesions after 207 days of gefitinib treatment. (D) New, minute, stationary nodular lung lesions after 613 days of gefitinib treatment. (E) First appearance of new brain lesions after 683 days of gefitinib treatment. (F) Stationary new brain lesions after 845 days of gefitinib treatment.

Results

One representative patient

A representative patient with primary lung adenocarcinoma had new indolent lung and brain lesions during EGFR-TKI therapy (Figure 1). The patient was treated with 2nd-line gefinitib, but new lung lesions were detected on

regular follow-up CT after 207 days of EGFR-TKI, and a new brain lesion after 683 days of EGFR-TKI, with controlled targeted lesions and no alterations in clinical manifestations. Because of the clinical stability, the patient continued to receive EGFR-TKI, but did not undergo radiation therapy after the new brain lesions were found due to personal considerations. Gefitinib was continued for 718 days after the new lung lesions were found, and then treatment was changed to non-EGFR-TKI chemotherapy due to PD deterioration, PD of the primary targeted lung, and new lesions. Survival time after discontinuing EGFR-TKI was 314 days. The patient did regain a stable clinical condition after continuing EGFR-TKI, even though the indolent new nodular lung and brain lesions waxed and waned (Figure 1A-F).

Clinical characteristics of patients with new lesions receiving EGFR-TKI

Thirty-seven patients with advanced-stage lung adenocarcinoma under EGFR-TKI treatment and with PFS of more than 6 months were analyzed (Table 1). Six (16.2%) were stage III and 31 (83.8%) were stage IV. Fifteen patients (40.5%) were treated with EGFR-TKI as 1st-line, 16 (43.2%) as 2nd-line and 6 (16.2%) as 3rd-line therapy. Eleven discontinued EGFR-TKI and received further chemotherapy, while 26 patients continued with the EGFR-TKI for more than 1 month after the appearance of new indolent lesions. Fifteen patients in the continuation group received gefitinib initially; 14 of the 15 patients continued gefitinib and 1 patient with new brain lesions switched to erlotinib. The other 11 patients in the continuation group who received erlotinib initially continued the same targeted therapy. There was no significant difference in PS between the continuation and discontinuation groups after the occurrence of new lesions.

Progression-free survival and overall survival

PFS with EGFR-TKI therapy was 252 days for the discontinuation group and 253 days for the continuation group (p=0.6389, hazard ratio (HR): 1.199, 95% CI: 0.5621-2.557) (Figure 2A). The median OS was 480 days and 771.5 days for the discontinuation and continuation groups, respectively (p=0.1526, HR: 1.824, 95% CI: 0.8005-4.155) (Figure 2B). Because a single phase was not observed in the survival curve of patients with continuous EGFR-TKI and there was contact with the curve of the control group at 900 days, further conditional median survival analysis was conducted. The patients of both groups were further divided into subgroups based on survival time <900 days and >900 days. For the subgroup with OS <900 days, the median OS was 480.5 days and 657.0 days for the discontinuation and continuation groups, respectively (p=0.0434, HR: 3.029, 95% CI: 1.034-8.875) (Figure 3A). For the patient subgroup with OS >900 days, the median OS was 1039 days and 1510 days for the discontinuation and continuation groups, respectively (p=0.0898, HR: 5.634, 95% CI: 0.7643-41.53) (Figure 3B). Median survival time after discontinuation of EGFR-TKI was 117.0 days in the discontinuation group and 143.0 days in the continuation group (p=0.9106, HR: 0.9581, 95% CI: 0.4538-2.023) (Figure 4A). Survival time after the appearance of definite new lesions was 152.0 days and 262.0 days in the discontinuation and continuation groups, respectively (p=0.0571, HR: 1.652, 95% CI: 0.7399-3.691) (Figure 4B).

Table 1. Patient Characteristics

Characteristics	Total	EGFR-TKI		
		Discontinuation	Continuation	*p* value
Patients, No.	37	11	26	
Age (year, mean ± SD)	60.8 ± 11.8	62.6 ± 10.2	60.0 ± 12.5	0.5962
Gender (male/female)	15/22	3/8	12/14	0.4657
Smoking (never/former)	25/12	8/3	17/9	1.0000
Stage (IIIB/IV)	6/31	3/8	3/23	0.3351
PS (0/1) at diagnosis	14/23	5/6	9/17	0.2628
PS (0/1) after new lesion	15/22	4/7	11/15	1.0000
Duration of EGFR-TKI (days, mean ± SD)	440 ± 267	358 ± 207	483 ± 281	0.133
Duration of EGFR-TKI after definite new lesions (days, mean ± SD)	116 ± 120	17 ± 8	157 ± 121	0.0005
Progression-free survival with EGFR-TKI (median days)		252	253	0.6389
Overall survival (median days)		480	771.5	0.1838
EGFR-TKI				0.7404
1st line	15	5	10	
2nd line	16	5	11	
3rd line	6	1	5	0.4444
Survival time after discontinuation of EGFR-TKI (median days)		117.0	143.0	0.9106
Survival time after definite new lesions (median days)		152.0	262.0	0.0571
Initial EGFR-TKI (G/E)	22/15	7/4	15/11	1.0000
Location of new lesions				0.3872
Lung	13	4	9	
Brain	7	3	4	
Liver	7	0	7	
Pleura	3	1	2	
Others	7	3	4	

Abbreviations: No., number; SD, standard deviation; PS, performance status; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; G, gefitinib; E, erlotinib

Others: bone (2), carcinomatosis peritonitis (2), spine (1), spleen (1), adrenal gland (1)

Characteristics of new lesions

For the 26 patients with continuous EGFR-TKI therapy, the characteristics of the new lesions and the additional therapy after these new lesions were found revealed that 9 patients had indolent new lesions in the lungs, 2 in the pleura, 4 in the brain, 7 in the liver, and 1 each in the peritoneum, bone, spleen, and adrenal gland (Table 2). Among the 23 patients with measurable lesions, 11 had lesions <10 mm, 9

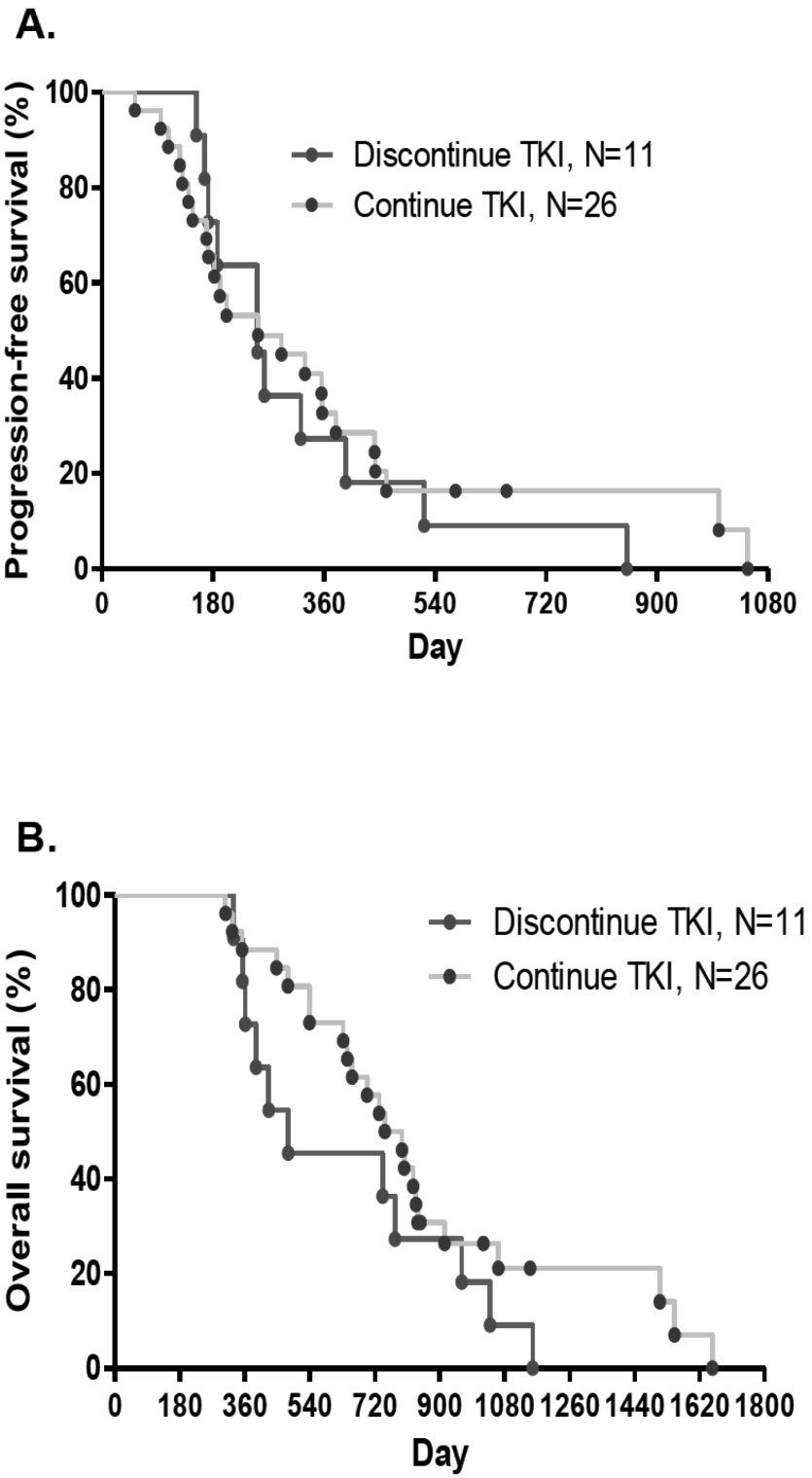

Fig. 2. Survival proportion traced using the Kaplan-Meier method. (A) Median PFS of the discontinuation and continuation groups receiving EGFR-TKI after the appearance of new lesions was 252 vs. 253 days, respectively (hazard ratio: 1.199, 95% CI: 0.5621-2.557; p=0.6389). (B) Median OS of the discontinuation and continuation groups receiving EGFR-TKI after the appearance of new lesions was 480 vs. 771.5 days (hazard ratio: 1.824, 95% CI: 0.8005-4.155; p=0.1526).

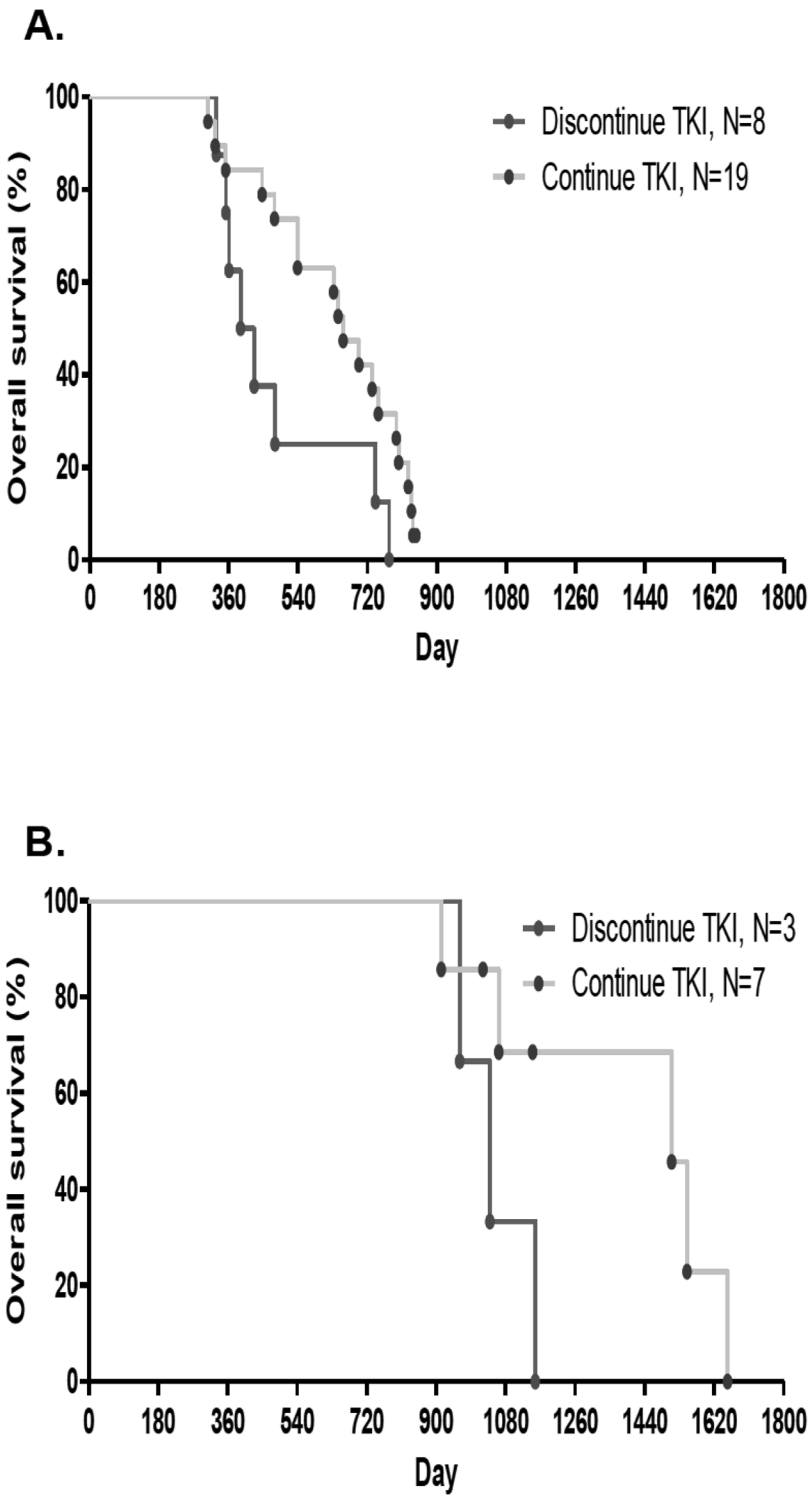

Fig. 3. Survival proportion traced with the Kaplan-Meier method. (A) Median OS <900 days in the EGFR-TKI discontinuation and continuation groups after the appearance of new lesions was 408.5 vs. 657 days (hazard ratio: 3.029, 95% CI: 1.034-8.875; p=0.0434). (B) Median OS >900 days in the EGFR-TKI discontinuation and continuation groups after the appearance of new lesions was 1039 vs. 1510 days (hazard ratio: 5.634, 95% CI: 0.7643-41.53; p=0.0898).

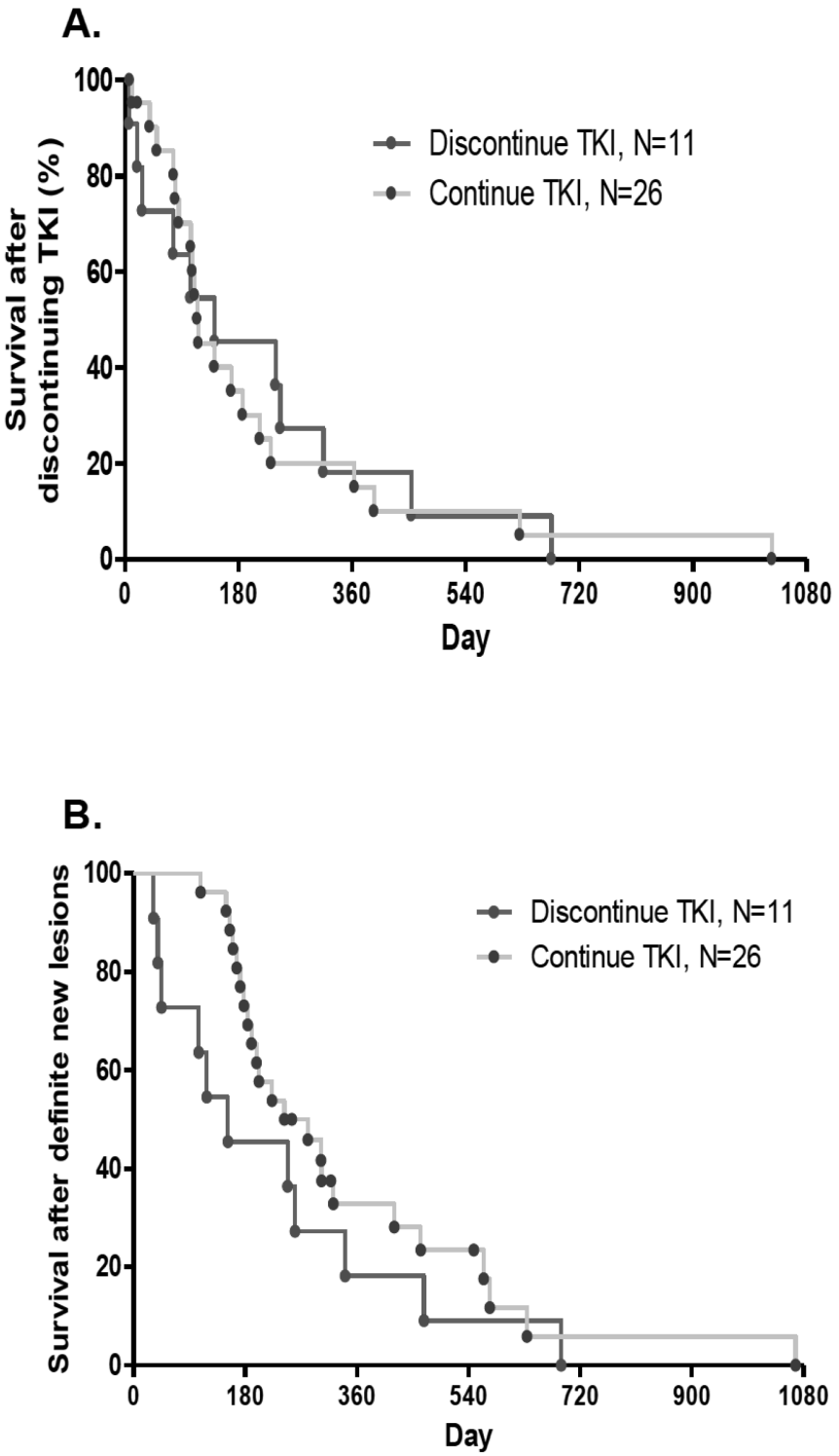

Fig. 4. Survival proportion traced using the Kaplan-Meir method. (A) Median survival time after discontinuation of EGFR-TKI in the discontinuation and continuation groups after the appearance of new lesions was 117 vs. 143 days (hazard ratio: 0.9581, 95% CI: 0.4538-2.023; p=0.9106). (B) Median survival after the occurrence of new lesions between the discontinuation and continuation groups was 152 vs. 262 days (hazard ratio: 1.652, 95% CI: 0.7399-3.691; p=0.0571).

Table 2. Characteristics of New Lesions and Therapy after New Lesions

Characteristics of New Lesions				
Location	Characteristics	Continuity	Discontinuity	*p* value
Lung	10 mm<size <20 mm, n=1, ground glass opacity	2	0	0.3443
	10 mm<size <20 mm, n=1, consolidation	1	0	0.4348
	10 mm<size <20 mm, n=1~2, nodular lesions	0	2	0.0524
	size<10 mm, n<10, nodular lesions	6	2	0.7409
Pleura	pleural effusion	1	1	0.5190
	pleural nodules, size (11 mm, largest), n=3	1	0	0.5096
Brain	size=17 mm, n=1, central necrosis, rim enhancement	1	0	0.5096
	size<10 mm, n=1, cystic lesion	1	0	0.5096
	size<10 mm, diffuse faint hyperdense nodules	1	0	0.5096
	size<10 mm, n<10, enhancing nodules	1	1	0.5190
	size<10 mm, n<10, tiny calcified spots	0	1	0.1191
	leptomeningeal carcinomatosis	0	1	0.1191
Liver	20 mm<size<25 mm, n=1~2, cystic lesions	2	0	0.3443
	10 mm<size<20 mm, n<5, cystic lesions	3	0	0.2399
	size<10 mm, n=1, cystic lesion	2	0	0.3443
Peritoneum	cancerous peritonitis, ascites	1	1	0.5190
Bone	rib and spine (cortical destruction)	1	1	0.5190
Spine	size<10 mm, n=1, nodule in cervical spinal cord	0	1	0.1191
Spleen	size=22 mm, n=1, solid tumor	1	0	0.5096
Adrenal gland	size=12 mm, n=1, central attenuation	1	0	0.5096

Additional Therapy after New Lesions in Continuation Group		Case No.
Radiation therapy	radiation therapy over brain	3
	radiation therapy over bone	1
Chemotherapy	chemotherapy with Taxotere (+erlotinib)	1
None	EGFR-TKI alone	21
Therapy after New Lesions in Discontinuation Group		
Radiation therapy	radiation therapy over brain	2
	radiation therapy over spine	1
Chemotherapy	systemic chemotherapy	7
Radiation therapy with chemotherapy	radiation therapy over brain with systemic chemotherapy	1

Abbreviations: No., number; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors

had lesions 10-20 mm, and 3 had lesions 20-25 mm. Four patients received additional radiation therapy and 1 had chemotherapy, while 21 continued with EGFR-TKI only.

The characteristics of the new lesions in the 11 patients with discontinued EGFR-TKI therapy showed that 4 patients had indolent new lesions in the lungs, 3 in the brain, and 1 each in the pleura, spine, peritoneum and bone. Among the 7 patients with measurable lesions, 5 had lesions <10 mm, and 2 had lesions 10-20 mm. Three patients received radiation therapy, 7 received chemotherapy alone and 1 underwent radiation therapy with chemotherapy after discontinuation of EGFR-TKI.

Discussion

In clinical practice, indolent new lesions with controlled primary targeted lung lesions are observed in patients with lung adenocarcinoma on EGFR-TKI treatment. Uncommonly long survival time and clinical stability are noted when continuing EGFR-TKI treatment, even after the first appearance of definite new lesions. Further analysis of patients with lung adenocarcinoma receiving EGFR-TKI therapy and with PFS of more than 6 months showed that OS and survival after the occurrence of definite new lesions in patients continuing EGFR-TKI therapy were not inferior to that of the discontinuation group. These results suggest a possible status of dynamic balance between tumor growth and cell death upon continuation of reversible EGFR-TKI therapy, as indicated by the central attenuated nodules and waxing and waning tumor size in the patients. Differences in histological growth patterns and molecular characteristics of lung adenocarcinoma may influence clinical outcome [18]. Some tumor cells may remain sensitive to EGFR-TKI beyond the occurrence of new lesions, which may complicate decision-making on alternative therapeutic agents when new lesions or PD occurs [13].

Most patients with EGFR-mutant lung adenocarcinoma develop PD after a median time of 10 to 16 months [19]. Acquired resistance to EGFR-TKI may involve a reversible "drug-tolerant" state, the mechanism of which needs to be established; furthermore, the contributions of specific resistance-conferring mutational and non-mutational mechanisms and the role of tumor cell sub-populations in drug resistance remain unclear [20]. A previous study reported that in NSCLC patients who initially responded but later developed acquired resistance to EGFR-TKI, gefitinib or erlotinib, discontinuing EGFR-TKI resulted in symptomatic progression and increased tumor size. Symptoms improved and tumor size decreased after restarting EGFR-TKI, suggesting that a proportion of cells in a resistant tumor cell population remain sensitive to EGFR, and that EGFR-TKI may be beneficial even after RECIST-defined PD [9]. A recent study also showed that EGFR-TKI re-treatment can be effective after failure of initial gefitinib treatment [12] and some EGFR-mutant lung cancer patients with PD who initially benefited from erlotinib or gefitinib experienced disease flare after discontinuing EGFR-TKI [10].

Re-treatment with erlotinib may be helpful for NSCLC patients who initially benefited from previous EGFR-TKI treatment and progressed after standard cytotoxic chemotherapy [11]. Another recent study showed that continuous EGFR-TKI administration following radiotherapy after PD in isolated CNS metastasis might be beneficial [8]. All of these suggest that local disease progression may not indicate acquired general systemic resistance. Compared

to the present study, definite new lesions are considered PD by RECIST 1.1, and continuous EGFR-TKI treatment may represent an effective option, with longer survival when indolent new lesions occur. Survival analysis is critically important to explore the proper management of NSCLC patients with local or indolent disease progression.

According to the Iressa Pan-Asia Study (IPASS) study and other similar reports [16-17,21], the efficacy of EGFR-TKI in terms of OS is similar between 1st- and 2nd-line uses. Since the number of patients retrieved from the Cancer Registry System was limited, the present study also enrolled patients with EGFR-TKI for initial 3rd-line therapy. Analysis of the survival curves of patients showed that PFS with EGFR-TKI did not differ significantly between groups. The median survival interval was longer in patients with continuous EGFR-TKI treatment after the first appearance of definite new lesions. Because of the limited number of subjects in the groups for analysis, statistical significance could not be attained. When the survival curve of patients with continuous EGFR-TKI treatment was separated from that of the patients who discontinued EGFR-TKI therapy, the length of survival after discontinuing EGFR-TKI did not differ with the overlap of the curves of groups despite delays in changing the therapeutic agent after new lesions. Nevertheless, OS was longer in the patients with continuous EGFR-TKI after the appearance of indolent new lesions compared to the survival curve of the discontinuation group. Hence, the data here suggest possible survival benefits from individualizing the extension of EGFR-TKI therapy. The absence of a single phase of the OS curve for patients with continuous EGFR-TKI, but a contact of the OS curves between groups at around 900 days suggest the heterogeneous characteristics of the groups [22]. Conditional survival analysis for patients with survival longer than 900 days reveals a marked separation of the curves, with median survival of 1039 days for patients with discontinued EGFR-TKI compared to 1510 days for those with continuous EGFR-TKI. Thus, patients with longer survival with EGFR-TKI therapy may have prolonged survival, but require more caution in agent alteration.

A review of the characteristics of new lesions in patients with continuous EGFR-TKI therapy reveals that smaller size and number of lesions, and nodular patterns and central low-attenuation on radiographic images suggesting tumor necrosis, may predict possible benefits with continuous EGFR-TKI. Compared with the continuation group, most measurable new lesions in the discontinuation group were also smaller and fewer, with nodular patterns especially in lung and brain lesions. There was no significant difference in the characteristics of the new lesions between the 2 groups. Response to additional local therapy in patients with prolonged EGFR-TKI after the occurrence of new lesions may also suggest a favorable outcome, consistent with previous reports [8,23]. Patients in the continuation group were receiving EGFR-TKI until progression of the primary target lung lesions or the appearance of new lesions with overall disease deterioration. Thus, definite new lesions are usually considered PD and a change in regimen is always suggested in clinical practice. However, as in previous reports and in the present study, continuous EGFR-TKI may still have clinical efficacy, although the mechanism warrants further investigation.

According to RECIST 1.0 (2000), the appearance of 1 or more new lesions is defined as

PD [14]. However, a number of questions led to the development of the revised RECIST 1.1 in 2009 [13], in which the description of new lesions was altered. Detecting new lesions is important during treatment, especially when the primary tumor lesion shows partial or complete response. The treatment plan will be altered if definite new malignant lesions are found. If new lesions cannot be identified unequivocally, for example because of the small size or osteoblastic reaction of bones after therapy, treatment may be continued until the next scheduled assessment. If follow-up images confirm new lesions, PD should be declared using the date of the initial scan [13]. Evaluation of new lesions may be difficult with CT if there is atelectasis, radiation pneumonitis, or subsequent fibrosis [24]. An FDG-PET scan is helpful in recognizing new lesions when it is compared to the initial FDG-PET scan and to follow-up CT scans to evaluate therapeutic response [25]. A negative FDG-PET at baseline with positive FDG-PET on follow-up is considered PD based on new lesions.

If FDG-PET is not performed at baseline, the interpretation of new lesions depends on a comparison of follow-up CT images [13]. As such, the first appearance of new lesions may not definitively indicate PD, but FDG-PET and low-dose high-resolution CT can help evaluate tumor volume and the speed of volume increase. In the present study, some new lesions remained stable or regained responsiveness to continuous EGFR-TKI, and OS was not hindered. This suggests that for patients on EGFR-TKI therapy with controlled primary targeted lesions, the policy of changing medication on the appearance of definite new lesions warrants further evaluation. Moreover, a practical adjunct test to evaluate tumor progression or systemic acquired resistance should be developed.

This study has some limitations. Only a small number of patients were enrolled, which made subset analysis difficult. The patients in this study also did not undergo EGFR mutation analysis because gene analysis was not used in clinical practice in the study institute before 2009. Nonetheless, only those patients with lung adenocarcinoma with response to EGFR-TKI for more than 6 months were selected for the study to reduce bias arising from the heterogeneous groups of lung cancer.

In conclusion, continuous EGFR-TKI does not hinder OS and survival time after the occurrence of new lesions in lung adenocarcinoma patients with controlled primary targeted lung lesions under EGFR-TKI treatment. Studies with a larger number of patients are needed to characterize the predictive factors of the benefit of continuous TKI and to establish a therapeutic strategy for this particular situation.

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肺腺癌病人產生新病灶時，持續使用 Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors 可能不會影響整體存活期

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陳濘宏　楊政達　蔡熒煌 **　劉劍英

背景：使用 Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors（EGFR-TKI）治療肺腺癌病人最終會因為抗藥性而使疾病惡化。然而，因為只有少數文獻探討當產生新病灶時，持續使用 EGFR-TKI 對存活時間之益處，本研究回顧性分析對於 Response Evaluation Criteria in Solid Tumors（RECIST）定義之疾病惡化狀況下可能的治療效果。

方法：本研究從 2005 年 1 月至 2009 年 11 月前瞻性記錄，回顧性分析 37 位肺腺癌病人。所有病人對於 EGFR-TKI 都至少有 6 個月之無惡化存活期，且原發部位肺腫瘤變小或穩定，而後產生新病灶。26 位病人持續使用而 11 位病人停止使用 EGFR-TKI。我們比較此二組病人之整體存活期，停止使用 EGFR-TKI 後之存活期和出現新病灶後之存活期。

結果：停止使用 EGFR-TKI 組整體存活期中位數為 480 天，繼續使用 EGFR-TKI 組整體存活期中位數為 771.5 天（p=0.1838）。停止使用 EGFR-TKI 後，存活期中位數在停止使用組為 117.0 天，在繼續使用組為 143.0 天（p=0.9106），而出現新病灶後之存活期中位數在停止使用組為 152.0 天，在繼續使用組為 262.0 天（p=0.0571）。

結論：肺腺瘤病人在 EGFR-TKI 治療下初始有反應，當出現新病灶時，繼續使用 EGFR-TKI 可能不會影響存活期。*(胸腔醫學 **2013; 28: 73-88**)*

關鍵詞：epidermal growth factor receptor tyrosine kinase inhibitors，新病灶，病情惡化，整體存活期，無惡化存活期

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Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma (P-MALToma) in a Patient with Chronic Pleural Effusion

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Pulmonary mucosa-associated lymphoid tissue lymphoma (P-MALToma) is a rare disease. We presented the case of a 72-year-old woman who was admitted to the hospital because of increasing dyspnea. Her chest roentgenogram revealed left upper lung consolidation complicated with left-side pleural effusion and enlarged right upper lobe consolidation, compared to a chest roentgenogram in 2007. She was diagnosed with low-grade extranodal marginal zone B cell lymphoma of mucosa-associated tissue of the lung (MALToma) based on results of a pathologic examination. *Candida albicans* was isolated from her left-side pleural effusion. Atypical lymphocytes with immunocytochemical anti-CD20 positivity were also isolated from her left-side pleural effusion. In tracing the patient's history, we found that the lesions had persisted for many years. Thus, we suggest MALToma is an indolent disease, but that any kind of infection will cause the MALToma condition to deteriorate. ***(Thorac Med 2013; 28: 89-95)***

Key words: pleural effusion, pulmonary mucosa-associated lymphoid tissue lymphoma (P-MALToma), clarithromycin

Introduction

Mucosa-associated lymphoid tissue lymphoma (MALToma) is a low-grade B-cell lymphoma which develops in the lungs, intestinal tract, salivary glands, thyroid glands, prostate, and other areas [1]. It is characterized by a proliferation of clonal marginal zone lymphocytes that invade their epithelial structures. The gastrointestinal tract is the most frequent primary location [2]. The occurrence of pulmonary MALToma is rare, accounting for only about 0.1% of malignant pulmonary tumors, and constitutes about 5% of all non-Hodgkin lymphomas (NHLs) and about 0.4% of all cases of lymphoma [3]. There is no age predilection for these tumors, but a female predominance has been noted [4-5]. Since the term MALToma

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was introduced in 1983 [6], chronic antigenic stimuli such as smoking, inflammatory diseases, autoimmune disease or a history of tuberculosis have been believed to be the etiological agents [7-8]. *Helicobacter pylori* had been firmly established as the causative pathogen responsible for gastric MALToma [9]. However, no such etiological infective agent has been identified in the lung so far.

Herein, we present the case of a patient with a history of old pulmonary tuberculosis and pulmonary MALToma that was diagnosed when she was admitted for pleural effusion.

Case Report

A 72-year-old ethnic Chinese woman presented with progressive exertional shortness of breath and dull discomfort on the left side of her chest that was unchanged with movement or inspiration. She had no other symptoms and had been well until 2 weeks before presenting at the hospital. She had a normal appetite and stable weight, and had no night sweats, fever or chills.

The patient's previous medical history included pulmonary tuberculosis with completed treatment; she had no hypertension or type 2 diabetes mellitus. She was a retired nurse and did not smoke or drink.

On physical examination, her body height was 144 cm, body weight, 46 kg, and body mass index, 22 kg/m^2. Her temperature was 36.6^{o}C, heart rate 98 beats per minute, blood pressure 144/88 mmHg, and oxygen saturation 98% while breathing ambient air. The neck was supple without lymphadenopathy, and the jugular vein was not engorged. Her legs revealed no pitting edema. There were rales in her left lung and decreased breathing sounds on auscultation.

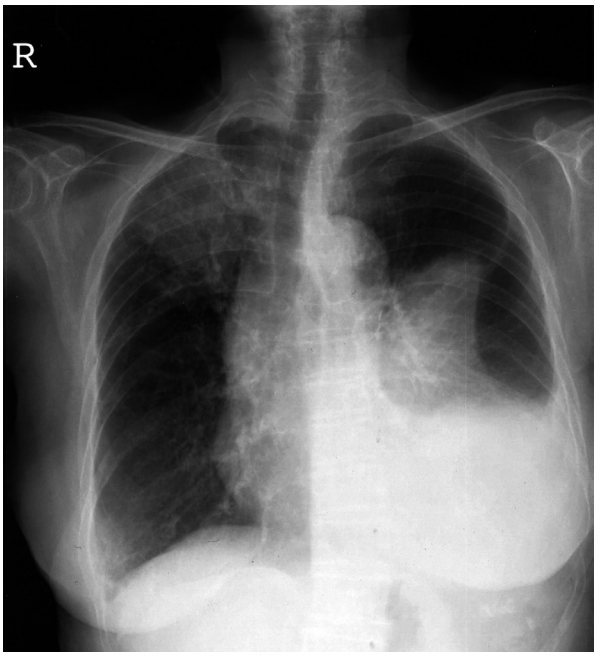

Fig. 1A. Chest roentgenogram on admission showed an enlarged consolidation and left-side pleural effusion.

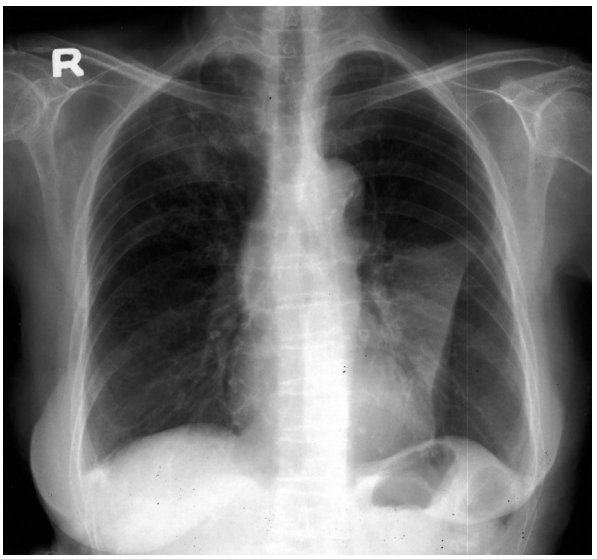

Fig. 1B. Chest roentgenogram 3 years before admission showed a small consolidation in the right upper and left lower lobes.

Chest roentgenogram on admission revealed left-side massive pleural effusion, and left upper and right upper lung consolidation (Figure 1A). A chest roentgenogram 3 years before had

shown a small consolidation in the right upper and left lower lobes (Figure 1B).

A laboratory workup showed the patient's hemogram, chemistry, electrolytes and tumor markers were within normal limits. The patient was found to have an exudate pleural effusion (lactate dehydrogenase-pleural fluid/lactate dehydrogenase: 150/212, total protein-pleural fluid/total protein: 5.5/8.0), which revealed atypical lymphocytes showing reactivity with antibody CD20, which was compatible with malignant lymphoma. *Candida albicans* was isolated from her left-side pleural effusion and non-tuberculosis Mycobacterium from her sputum. A pig tail was inserted for left-side pleural effusion drainage (Figure 1C) and anti-fungal medication was prescribed.

A flexible fiber-optic bronchoscopy revealed normal patent and smooth bronchial mucosa of the bilateral bronchus. Pathological diagnosis was obtained by a computed tomography-guided percutaneous right upper lung biopsy. Immunohistochemical staining revealed all tumor cells stained positive for CD20, CD79α and BCL-2, confirming the diagnosis of MALToma (Figure 2A-E).

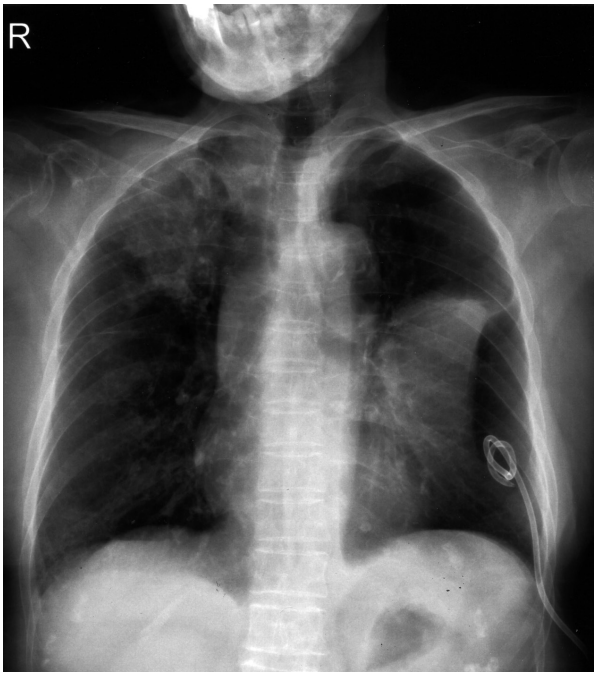

Fig. 1C. Chest roentgenogram of post-pig tail insertion for left-side massive pleural effusion drainage.

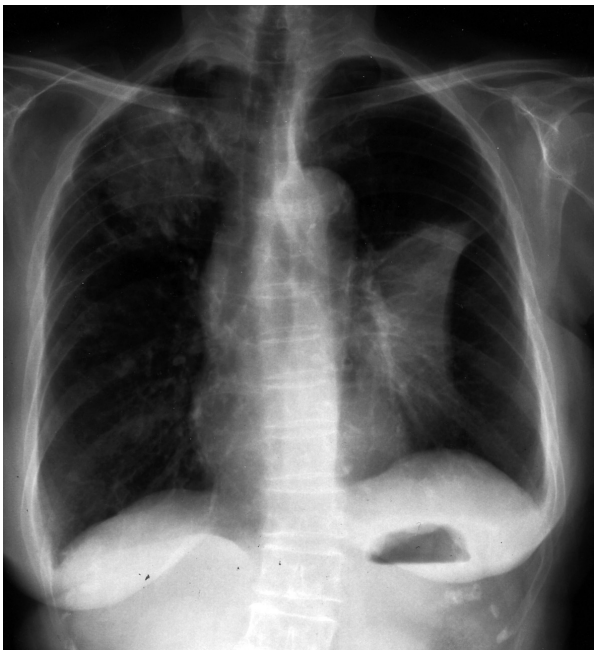

Fig. 1D. Chest roentgenogram showing the left-side pleural effusion had subsided.

Even though the patient and her family refused further chemotherapy or radiotherapy, her left-side pleural effusion subsided when she was discharged (Figure 1D). The patient remained well 1 year after discharge and was followed regularly under treatment with clarithromycin 500 mg/day.

Discussion

It has been reported that pulmonary (P-) MALToma is a diverse disease with an indolent nature [3]. Most MALToma patients are asymptomatic during the initial diagnosis. Yong *et*

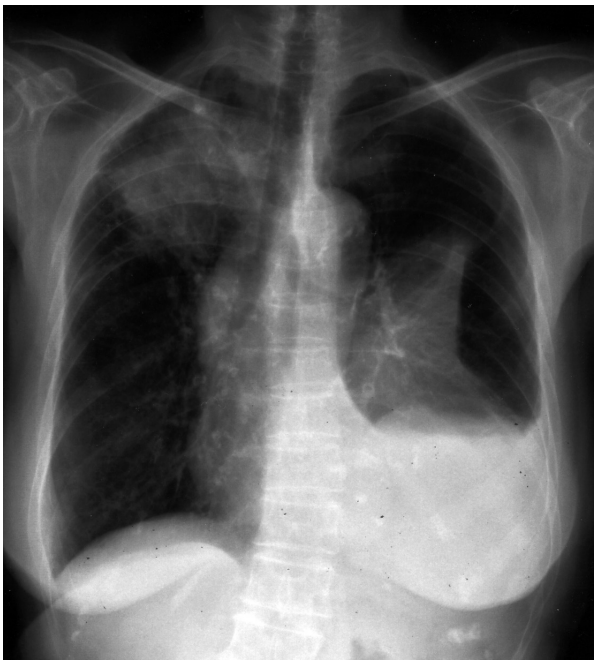

Fig. 1E. Chest roentgenogram after a year of CAM treatment showing the consolidation size was unchanged.

al. reported that 33.3% of their patients were asymptomatic and were discovered incidentally [10]. Huang *et al*. also found that respiratory symptoms were common, but constitutional symptoms such as fever, fatigue and body weight loss were not [8]. MALToma has a heterogeneous appearance on chest roentgenograms, and its most common radiological presentations are pulmonary masses, mass-like areas of consolidation, and single or multiple nodules [11]. Controversy regarding the involvement of unilateral or bilateral disease has been noted [4,12-13]. Previous studies reported that pleural effusion and mediastinal or hilar lymphadenopathy was rare, but our patient presented left-side massive pleural effusion [4,12-14]. The patient's MALToma was discovered incidentally. She had been asymptomatic prior to her hospitalization, although her chest roentgenogram 5 years prior to this admission revealed a consolidation-like mass in the right upper and left lower lobes. It has been reported that the interval between the first clinical or radiological manifestation and diagnosis was from 5 months to 8 years [15-16]. Therefore, P-MALToma is an indolent disease with the potential of spontaneous regression, as previously reported [7,15-17]. Hence, a watch-and-wait policy could be considered as the initial management of P-MALToma in asymptomatic patients [18].

Infection has been reported to be one of the most important pathogenesis of P-MALToma [3,19]. Our patient was asymptomatic prior to this hospitalization, when left-side massive pleural effusion was noted. *Candida albicans* was isolated from the left-side pleural effusion at that time. This allowed us to ponder the relationship between the infection and MALToma. Infection was believed to have deteriorated the MALToma condition, with pleural effusion ensued. This phenomenon became evident at her hospitalization a year later because of her acute bronchitis. The bilateral lobar masses remained the same size compared with the chest roentgenogram the year before (Figure 1E). Her left-side pleural effusion was an exudate (WBC: 2320/uL, lymphocytes: 95%, neutrophils: 2%, PF-LDH/LDH: 90/110, PF-TP/TP: 3.6/5.5). This was consistent with most of what has been reported, that infection is one of the inducers of MALToma [20].

Several researchers suggested there is a favorable response to surgery, chemotherapy, or radiotherapy alone or in combination [18]. However, there is no standard regimen for P-MALToma. Ishimatsu *et al*. reported 2 cases with P-MALToma successfully treated with clarithromycin (CAM) (200 mg/d) [9]. Therefore, we prescribed CAM (500 mg/d) for our

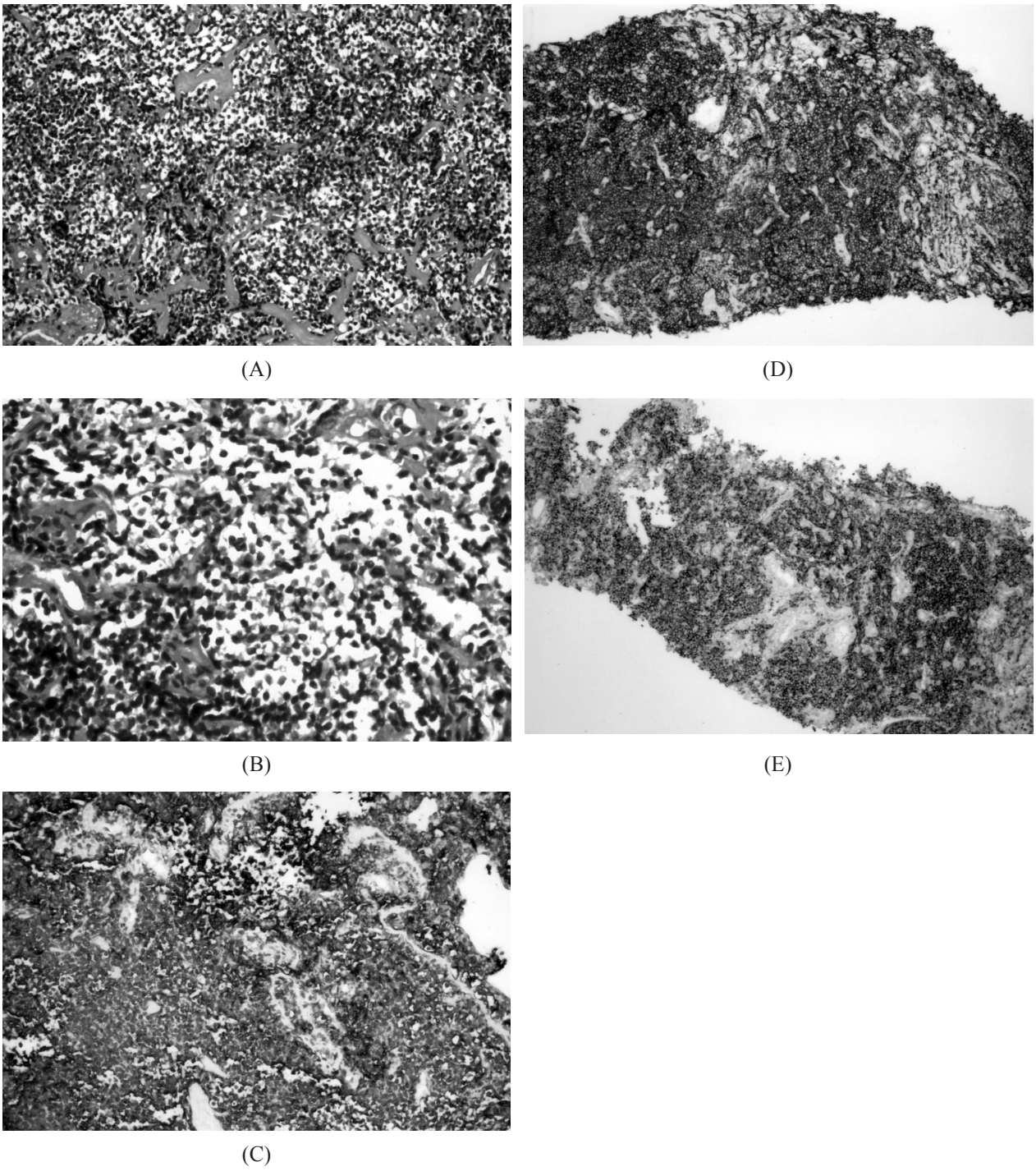

Fig. 2. (A) Histologic examination of pulmonary mass lesion in the right upper lobe. Diffuse infiltration of small lymphoid cells to the follicles (H&E stain; 200X). (B) Lymphoid cells infiltrated into the mucosal epithelium of the bronchus (lymphoepithelial lesion) (H&E stain, 400X). (C) Immunohistochemical stain for CD20 (200X) showed a positive reaction. (D) CD79α (100X) showing almost exclusively B lymphocytes exhibiting a brownish reaction product. (E) Immunohistochemical stain for Bcl-2 (100X) showing a positive reaction

patient and followed up regularly. The size of the P-MALToma remained the same without deterioration and she was in stable condition. Although our experience with CAM was successful, further clinical randomized controlled trials with a larger number of patients are needed to support this finding.

Conclusion

The clinical manifestations of P-MALToma are diverse. MALToma is a malignant tumor but has indolent behavior and a relatively good prognosis. Any kind of infection might play a role in the pathogenesis and its management.

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肺黏膜相關淋巴組織淋巴瘤（MALT 淋巴瘤）於慢性肋膜積水和眞菌感染的病人

林縵婷 * 吳子卿 * 吳銘芳 *,** 賴銘淙 *** 曹世明 *,****

黏膜相關淋巴組織淋巴瘤（MALToma）是一種低度惡性度的 B 細胞淋巴瘤。它可生長在胃、肺、唾液腺、甲狀腺或前列腺。肺部黏膜相關淋巴組織的淋巴瘤（p-MALToma）是個很少見疾病。雖然 MALToma 是惡性腫瘤，但是其臨床表現及特性是屬於進展緩慢的疾病（indolent）且預後良好。

我們報告一位 72 歲女性罹患 MALToma 被診斷的時候是，以左側的大量肋膜積水來表現。一年來，病人除一開始的抗黴菌藥與長期服用 clarithromycin 外並未接受任何化學治療，胸部 X 光至今無明顯變化。正如幽門桿菌感染已確定為胃部 MALToma 的致病因子，結核菌感染也被認為在 p-MALToma 伴演重要角色。因此，本文個案患有陳舊性結核病與慢性肋膜積水更可以讓我們思考慢性感染與 MALToma 之間的關係。*(胸腔醫學 **2013; 28: 89-95**)*

關鍵詞：肋膜積水，肺部黏膜相關淋巴組織淋巴瘤（p-MALToma)，克拉霉素

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Back Pain, Multi-segmental Spondylitis, and Lung Consolidation – A Rare Constellation of Actinomycosis

Chor-Kuan Lim, Hao-Chien Wang, Jin-Yuan Shih, Huey-Dong Wu*, Chong-Jen Yu

Actinomycosis is a rare pulmonary infection that can mimic a variety of chronic suppurative lung diseases or lung tumors. Involvement of the vertebral column is very rare. In this article, we report the case of a 28-year-old man who presented with upper back pain for 6 months; radiological examinations showed right upper lung consolidation and multi-segmental spondylitis of the thoracic spine. Chronic inflammation was observed during ultrasonography-guided aspiration and conventional computed tomography-guided biopsy. Wedge resection via video-assisted thoracoscopic surgery of the right upper lung and histopathological examination of the tissue established a diagnosis of actinomycosis. The patient was treated with intravenous penicillin G for 14 days followed by oral amoxicillin/clavulanic acid for 3.5 months, without any sequelae. Actinomycosis infection is rare; therefore, a diagnosis can be difficult to attain. A high degree of clinical suspicion, an early diagnosis, and appropriate treatment may prevent morbidity considerably. ***(Thorac Med 2013; 28: 96-101)***

Key words: pulmonary actinomycosis, spondylitis

Introduction

Actinomyces comprises a group of aerobic or microaerophilic Gram-positive bacilli that are commensal inhabitants of the oral cavity and gastrointestinal and urogenital tracts in humans [1]. The diseases caused by Actinomyces are classified according to the infection sites: orocervicofacial, thoracic, abdominopelvic, central nervous system, musculoskeletal, and disseminated [2]. The lung is an uncommon infection site, and vertebral column involvement resulting in spondylitis is rarer. Actinomycosis shares many similar clinical features with chronic suppurative lung infections, such as tuberculosis (TB) or fungal infection, and lung cancer [3]. Establishing a definite diagnosis of actinomycosis is challenging and often delayed owing to the fastidious nature of the bacteria. We report a case of pulmonary actinomycosis complicated with spondylitis in a 28-year-old man with upper back pain for 6 months.

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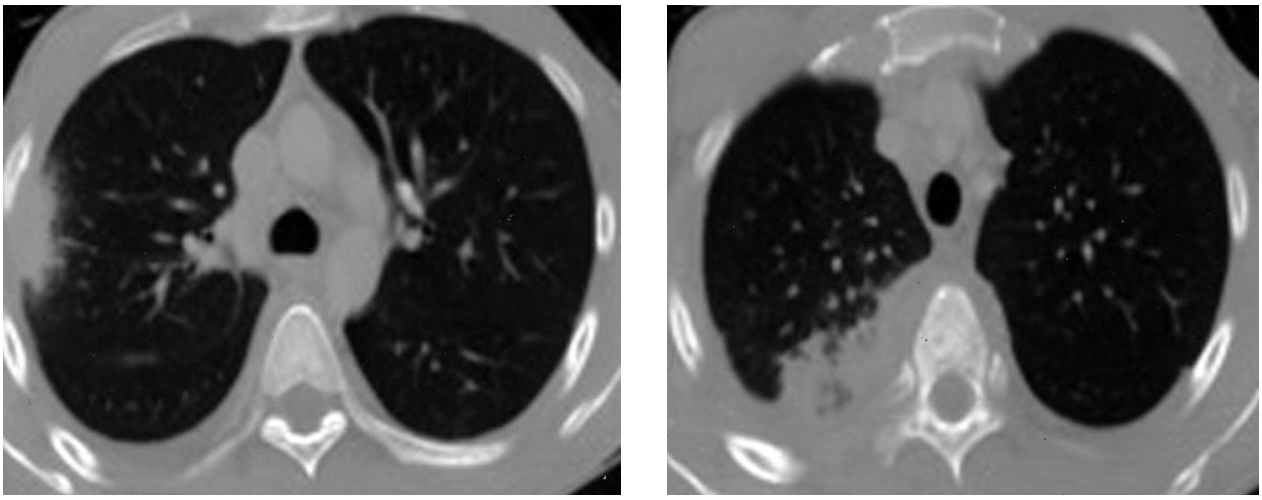


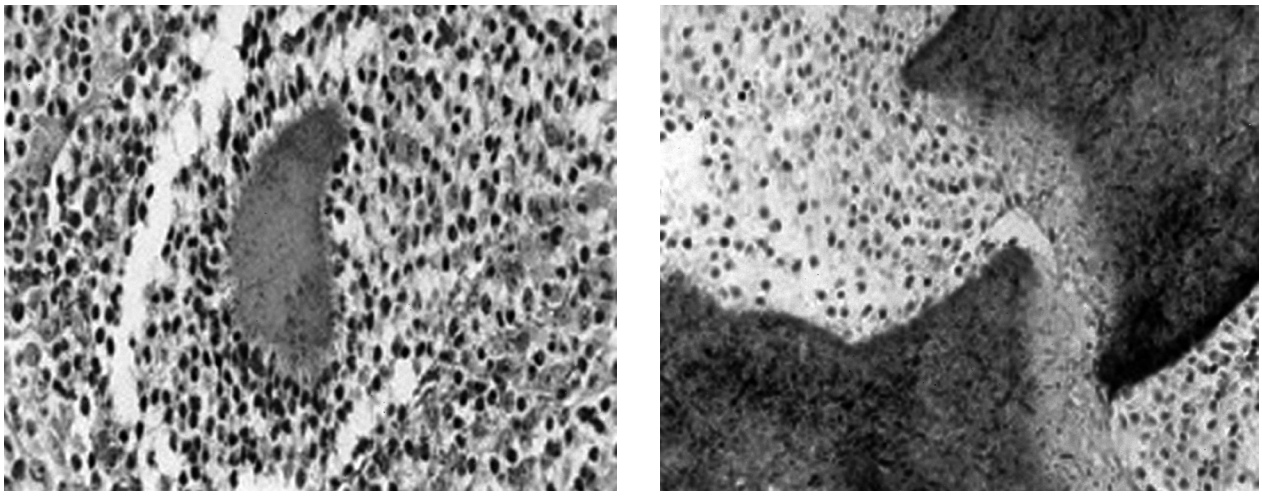
(A) (B)

Fig. 1. Consolidation of the (A) lateral and (B) posterior aspect of the right upper lung.

Case Report

This 28-year-old man was a merchandiser in South Africa. He was diagnosed with Type 1 diabetes mellitus when he was 13 years old and had been treated with insulin since then. He experienced upper back pain for 6 months, and no conclusive diagnosis could be reached in South Africa. Therefore, he visited a local hospital in Taiwan, where chest radiography showed patchy opacity at the right upper lung. Chest computed tomography (CT) showed consolidation at the lateral and posterior aspects of the right upper lobe, and soft-tissue masses surrounding the paraspinal region from vertebrae T2 to T4, with mild bone destruction (Figures 1A, 1B). Based on the radiographic images, pulmonary TB with cold abscess formation was suspected.

The patient visited our chest medicine outpatient department for a second opinion and was admitted for further work-up. Upon physical examination, the breathing sound was clear. Neurological examination revealed no deficits or tender point at the upper back. A hemogram showed leukocytosis, with the white blood cell count at 16.06 K/μL, and serum biochemical analysis revealed an elevated C-reactive protein level (2.11 mg/dL) and HbA1c of 6.9%. Chest ultrasonography showed a subpleural consolidation at the posterior aspect of the right upper lung. The results of the ultrasonography-guided aspiration examination showed an absence of bacterial growth or malignant cells. Therefore, CT-guided biopsy was performed, and pathologic examination of the specimen showed chronic inflammation. Microbiological study revealed an absence of bacterial growth. For a definitive diagnosis, the patient underwent wedge resection of the right upper lung via video-assisted thoracoscopic surgery. Pathologic examination of the specimen showed the presence of multiple foci of acute inflammation with sulfur granules, characterized by radiating eosinophilic club-like rods at the periphery (Figure 2A). Gram stain revealed Gram-positive



(A) (B)

Fig. 2. (A) Splendore-Hoeppli phenomenon. Prominent eosinophilic, club-like rods radiate from the sulfur granules. The surrounding area shows acute inflammation. (B) Thin filamentous branching bacilli (hematoxylin and eosin stain; magnification: 200×).

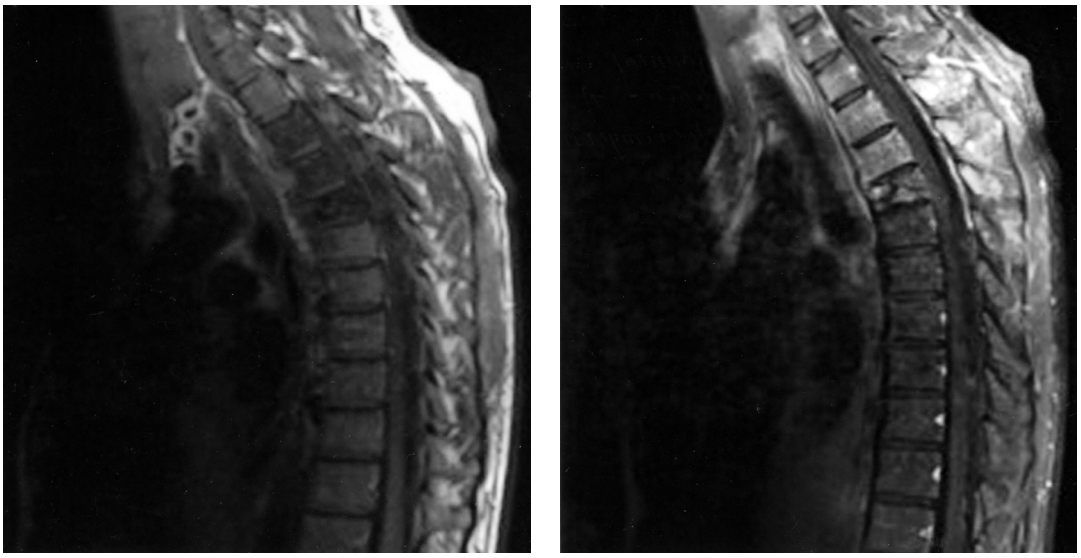
bacilli with thin filamentous branching (Figure 2B); therefore, actinomycosis infection was suspected. The tissue culture yielded no growth. In addition, magnetic resonance imaging of the spine showed infiltrative soft-tissue lesions at the posterior aspect of the right upper lung and the paraspinal region, at the T2-T4 level, with marrow edema or hyperemia, suggestive of spondylitis; a compression fracture at T4 was noted (Figures 3A, 3B). Thus, pulmonary actinomycosis complicated with spondylitis was confirmed.

During hospitalization, the patient developed a fever, and cefepime was empirically administered for a suspected nosocomial infection. After actinomycosis was confirmed, cefepime was replaced with penicillin G sodium 3 MU, administered intravenously every 4 hours. This regimen was replaced with oral-form amoxicillin/clavulanic acid 14 days later. Chronic periodontitis was also diagnosed during hospitalization. After completing a 4-month antibiotic treatment, the patient's upper back pain had ameliorated and chest CT showed regression of pulmonary consolidations and soft-tissue masses at the paraspinal region. The patient returned to his premorbid status without any sequelae.

Discussion

Actinomycosis is an indolent and slowly progressive disease characterized by abscess formation, tissue fibrosis, and draining sinuses. It is caused by Gram-positive, non-spore-forming bacteria belonging to the *Actinomycetaceae* family (genus *Actinomyces*) [4]. Disruption of tissue integrity through trauma or mucosal lesions is essential for the infection, enabling the bacteria to invade local regions or organs, and subsequently become pathogenic.

Actinomycosis affects virtually any body site, with 55-60% of all actinomycosis cases involving the orocervicofacial region, which is the most common infection site. Other infection sites include abdominopelvic (20%), pulmonary



(A) (B)

Fig. 3. (A) Decreased marrow signal intensity on T1-weighted images at the T2-T4 level. (B) Compression fracture at T4.

(15%), central nervous system (2%), cutaneous (rare), musculoskeletal (rare), and disseminated (rare) [2].

Several risk factors predispose individuals to develop actinomycosis. Men are 3 times more likely to be infected [5], except with pelvic actinomycosis, which mainly affects women [6]. Other risk factors include an age of 20-60 years, the use of intrauterine devices, poor oral hygiene, immunocompromised status, steroid use, human immunodeficiency virus infection, leukemia, lung and renal transplantation, alcoholism, and diabetes mellitus [4]. Our patient was a 28-year-old man with Type 1 diabetes mellitus and chronic periodontitis.

The diagnosis of actinomycosis requires a high degree of clinical suspicion, since it is a chronic, slowly progressive disease and patients with actinomycosis often have nonspecific clinical manifestations. Nevertheless, some "warning signs", such as slow progression, chronicity, mass-like features, development of sinus tracts (which heal and re-form), progression through tissue planes, and refractory or relapsing infection after a short course of antibiotics, may help alert clinicians during daily practice [4]. Moreover, owing to the fastidious nature of the bacteria, bacterial confirmation of a clinicopathological diagnosis is usually difficult to attain [7]. Previous antibiotic treatment, overgrowth of concomitant organisms, or inadequate methodology may account for the high failure rate of isolation [7]. On histopathological examination, the presence of Gram-positive filamentous organisms and sulfur granules are strongly suggestive of actinomycosis, because sulfur granules are a pathological characteristic of actinomycosis, appearing as colonies of organisms with round or oval basophilic masses with radiating eosinophilic club-like formations at the periphery on hematoxylin-eosin staining. Nonetheless, sulfur granules may also be found in nocardiosis, chromomycosis, eumycetoma, and botryomycosis, albeit very rarely [1].

Actinomycosis can be treated by a variety of antibiotics, such as ß-lactams (including benzylpenicillin, amoxicillin, ceftriaxone, meropenem, and piperacillin-tazobactam), doxycycline, clindamycin, erythromycin, and clarithromycin. Treatment duration depends on the initial burden of the disease, the outcome of resectional surgery, and the response of the patient to treatment [8]. There is no consensus on the optimal treatment duration and not all patients require therapy for 6-12 months, as traditionally recommended. Our patient received treatment for 4 months; the last outpatient follow-up revealed no relapse.

In conclusion, actinomycosis is a rare but curable disease. Prompt and accurate diagnosis is dependent on a high degree of clinical suspicion of the disease. With appropriate treatment, the prognosis is favorable. Further, actinomycosis should be considered in a patient with lung consolidation and back pain, even though pulmonary actinomycosis with spondylitis is rarely encountered.

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背痛，多節脊柱炎，肺實質化 — 放線菌感染的罕見匯集

林祖權　王鶴健　施金元　吳惠東*　余忠仁

放線菌病是一種罕見的肺部感染，它的臨床表現可和各種慢性化膿性肺部疾病或肺癌相近。放線菌於脊柱的感染更是罕見。本文描述一位 28 歲的男性主訴上背部疼痛六個月。胸部 X 光及電腦斷層顯示右上肺實質化和胸椎多節段脊柱炎。右上肺的病兆於超音波導引和電腦斷層導引下穿皆無法獲得確診。病患接受楔形切除後證實為放線菌感染。病人接受了四個月的盤尼西林類抗生素治療，症狀完全緩解，並不留任何後遺症。臨床上常難以確診放線菌感染。高度的臨床懷疑，早期的診斷和適當的治療才能預防嚴重的併發症。*(胸腔醫學 **2013; 28: 96-101**)*

關鍵詞：放線菌，放線菌感染，肺實質化

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Treating Early-Stage Lung Cancer with Radiofrequency Ablation – A Case Report

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The prevalence of lung cancer is high in Taiwan. For patients with early-stage lung cancer, surgical resection is the standard treatment. In clinical practice, some patients are poor surgical candidates because of old-age, poor cardiopulmonary functional reserve or other comorbid diseases. Radiofrequency ablation (RFA) has been used to treat hepatocellular carcinoma for a decade with good results, and recently, it has been utilized for local control of lung cancers. We report an elderly patient with early-stage adenocarcinoma of the lung. Her comorbid conditions of diabetes mellitus, rheumatoid arthritis and poor cardiopulmonary function made the risk of surgery high and unacceptable. The patient was treated with RFA and was followed up for 1 year with a good response. RFA-related complications such as pneumothorax, hemoptysis, pain and pleural effusion are readily handled clinically. The efficiency of RFA depends on tumor size. A tumor diameter of less than 3 cm yields good local control. Computed tomography and positron emission tomography are usually used to evaluate the treatment outcome. RFA is a minimally invasive treatment, and preserves the patient's pulmonary function. Repeat treatments are also possible. ***(Thorac Med 2013; 28: 102-109)***

Key words: lung cancer, radiofrequency ablation

Introduction

Lung cancer is the most common cause of cancer mortality in Taiwan, and accounts for 20% of cancer-related deaths annually for both men and women. Surgical resection offers the best chance for cure of early-stage non-small cell lung cancer (NSCLC) patients. However, the majority of NSCLC patients is diagnosed late with advanced-stage disease, and they are therefore poor candidates for surgery. In addition, 1/5 of patients with early-stage NSCLC are too weak to receive an operation because of medical comorbidities, such as poor heart and lung condition, old age, and diabetes mellitus (DM). Thermal ablation such as radiofrequency ablation (RFA) and microwave ablation (MWA) are emerging as promising treatment options for

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local tumor control. Early clinical experience and a rapidly growing body of prospective clinical trials, primarily involving medically inoperable patients, are demonstrating encouraging effectiveness and safety outcomes [1]. In Taiwan, RFA has been applied for local ablation of liver cancer since 2002 [2]. The favorable results have made it widely accepted as an alternative to resection in case of small, resectable or even un-resectable liver cancers [1]. However, this technique has rarely been applied to thoracic tumors and has seldom been reported in Taiwan, which may be due to the frequent procedure-related complications such as pneumothorax, bleeding or asphyxia [3]. We address this issue and report a case with early-stage primary lung cancer successfully treated with RFA.

Case Report

The patient was a 79-year-old female. She had type 2 DM for more than 25 years and was currently using an oral hypoglycemic agent to control her DM. In addition, she was diagnosed with rheumatoid arthritis 2-3 years ago, but no regular medication was prescribed. She presented with a 2-week history of productive cough with whitish sputum. The patient also complained of shortness of breath and intermittent wheezing. The chest X-ray (CXR) showed a solitary pulmonary nodule in the right upper lung field (Figure 1A). Computed tomography (CT)-guided biopsy proved it to be adenocarcinoma. Clinical staging based on chest CT, brain CT and positron emission tomography (PET) disclosed T1bN0M0, stage IA (Figures 2A and 3A). The tumor had a dumpling shape measuring 20 × 15 mm. Because of the patient's age, comorbidities, and poor lung function (forced expiratory volume in the first second was 0.76 liter, 45% of predicted value), surgery was not feasible. We performed RFA 2 weeks after diagnosis (Figures 2A and B) and after receiving approval from the ethics committee.

During RFA, the patient was lying in the supine position, properly restricted with a vacuum mattress and sedated with Dormicum intravenously. After local disinfection and local anesthesia with 6 ml of 2% xylocaine, a 15 cm long antenna probe (AP) was used to penetrate the chest wall into the right apical lung through the tumor. The process was smooth and no pneumothorax or other complications occurred. She went home 2 days later. Chest CT was performed 2, 4 and 8 months later, and revealed that the tumor size had decreased gradually (from about 40 × 20 mm to 35 × 18 mm and 27 × 13 mm at 2, 4 and 8 months, respectively). A PET/CT scan was arranged 6 and 12 months after RFA (Figures 3B and C), and a progressive decrease in the standardized uptake value (SUV) was observed (Figures 3A, B and C). We concluded there was good local control of the primary lung lesion.

Discussion

RFA ablates tissue by heating it to cytotoxic temperatures [4-5]. An AP connected to an electric power source is inserted through the chest wall into the lung tumor to generate radiofrequency waves to agitate the water molecules around the AP, producing heat and damage the surrounding tumor tissue. Temperatures exceeding 60°C will cause relatively instantaneous cell death, while temperatures between 50°C and 60°C will induce coagulation and cell death in a matter of minutes. However, applying RFA to lung cancer tissue has a few disadvantages compared to its use with liver tumors, such as

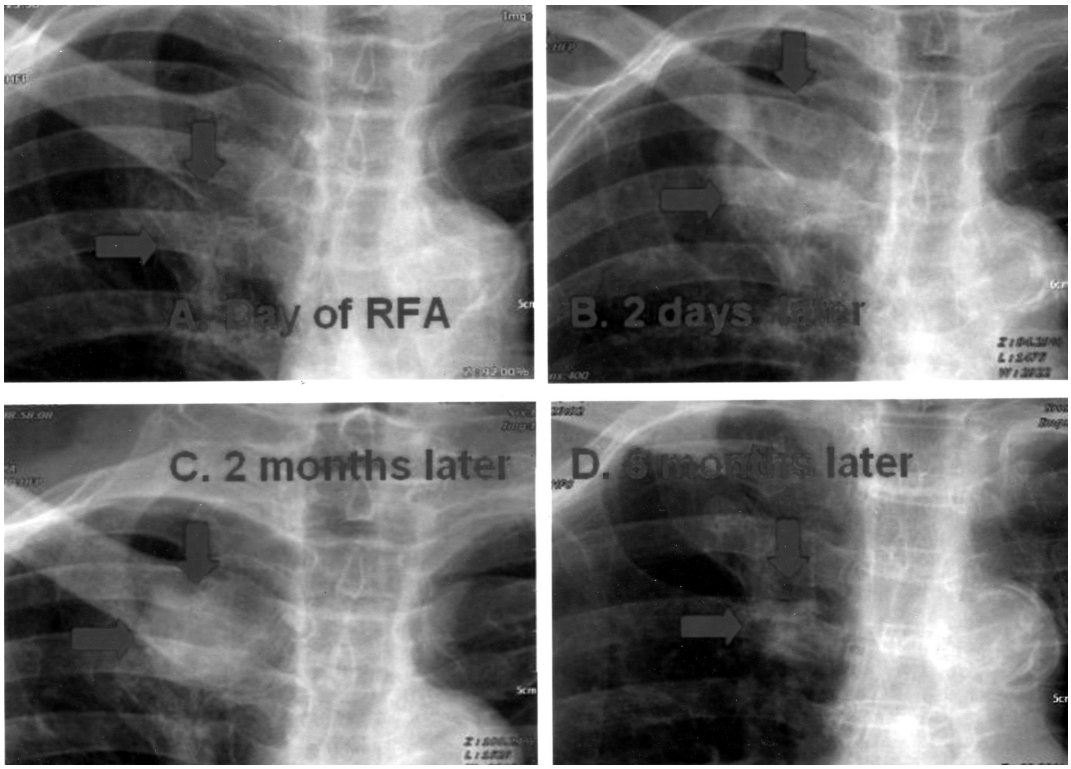

Fig. 1. (A) CXR before RFA. (B) Two days after RFA, the tumor is enlarged and engulfed with GGO. (C) Two months after RFA, the tumor has contracted, but is bigger than before RFA. (D) Six months later, the tumor has shrunk.

reducing heat conductivity and enhancing of heat removal. Air-filled tissue may insulate heat conduction, thereby reducing thermal transmission from the AP during lung RFA. Given the same energy, the RFA ablation zone is smaller for an air-filled lung than for solid liver tissue. On the other hand, the lung is highly perfused with low resistance to pulmonary blood flow. During RFA, heat generated from the AP will be absorbed by the surrounding tissue or removed by the blood flow. This excessive heat loss from the blood vessels is called the "heat sink effect" [6]. This effect may cause incomplete ablation when a tumor is close to or in direct contact with a vessel larger than 3mm. RFA will damage tissue and lead to coagulation necrosis when a temperature of 60-100°C is maintained. Excessive temperatures above 105°C may damage tissue and cause charring, and the increased electric impedance thus limits the electric flow and decreases coagulation necrosis volumes. This can also prevent withdrawal of the AP and practitioners need to be aware that this could lead to a serious complication [7].

RFA will achieve total necrosis and complete local control when a tumor is less than 3 cm in diameter and at the periphery of the lung. In this case, the vessels were tiny and scarce and the "heat sink effect" was negligible, so the temperature was homogenously distributed and maintained throughout the procedure. When the tumor diameter is between 3 and 5 cm, the therapeutic effect of RFA worsens and the local recurrence rate increases. In a systematic

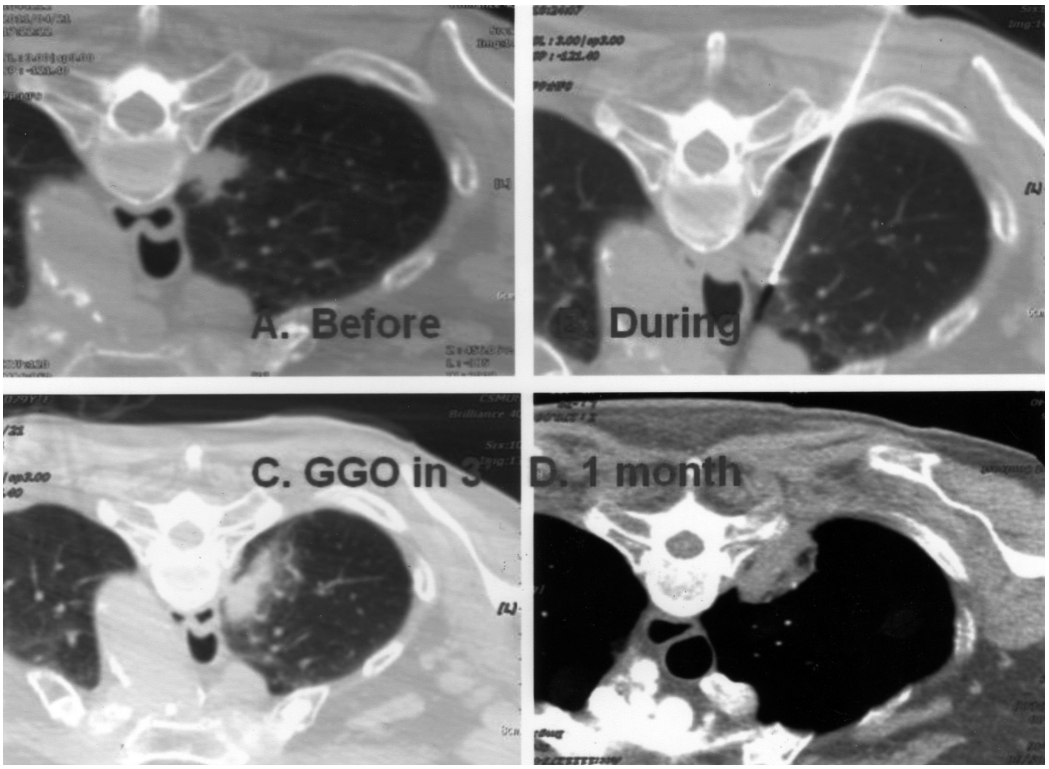

Fig. 2. (A) Chest CT scan before RFA showing a dumpling-shaped nodule 20 × 15 mm along the subpleural region of the right upper lobe. (B) The RFA probe penetrating the tumor at the medial side. (C) Three minutes after RFA, GGO developed around the tumor. (D) One month later, the previously concave dumpling-shaped tumor had swelled and the peripheral margin had become a straight line. This reflects the extent of the thermal damage by the RFA AP.

review, local recurrence rates of 3-38.1% (median, 11.2%) and complete tumor necrosis rates of 38-97% (median, 90%) were reported [8]. In our patient, a peripheral dumpling-shaped tumor (Figures 2A and B) was ablated. Ground glass opacity (GGO) (Figure 2C) appeared around the tumor immediately after RFA, implying thermal damage exceeded the tumor volume. The serial CXR (Figures 1C and D) also demonstrated an initial swelling of the soft tissue density followed by progressive shrinkage. The follow-up chest CT 1 month after RFA (Figure 2D) showed that the previously concave dumpling-shaped tumor had swelled. The peripheral margin became a straight line reflecting the border of tissue damage, which was 15 mm distal and parallel to the AP. The follow-up PET scan revealed a progressive decrease in the fluorodeoxyglucose (FDG) uptake, indicating complete necrosis after RFA.

RFA has some advantages, namely that it can be repeated whenever local progression appears; on the other hand repeat surgery or radiation therapy is impossible. RFA is also minimally invasive, has a low risk of complications, requires a shorter hospital stay and preserves the lung function well. When combined with radiotherapy, there is a beneficial synergic effect without additional major toxicities [9-10].

GGO develops immediately after RFA and persists for a few months. Anderson assessed the usefulness of the GGO margin for the pre-

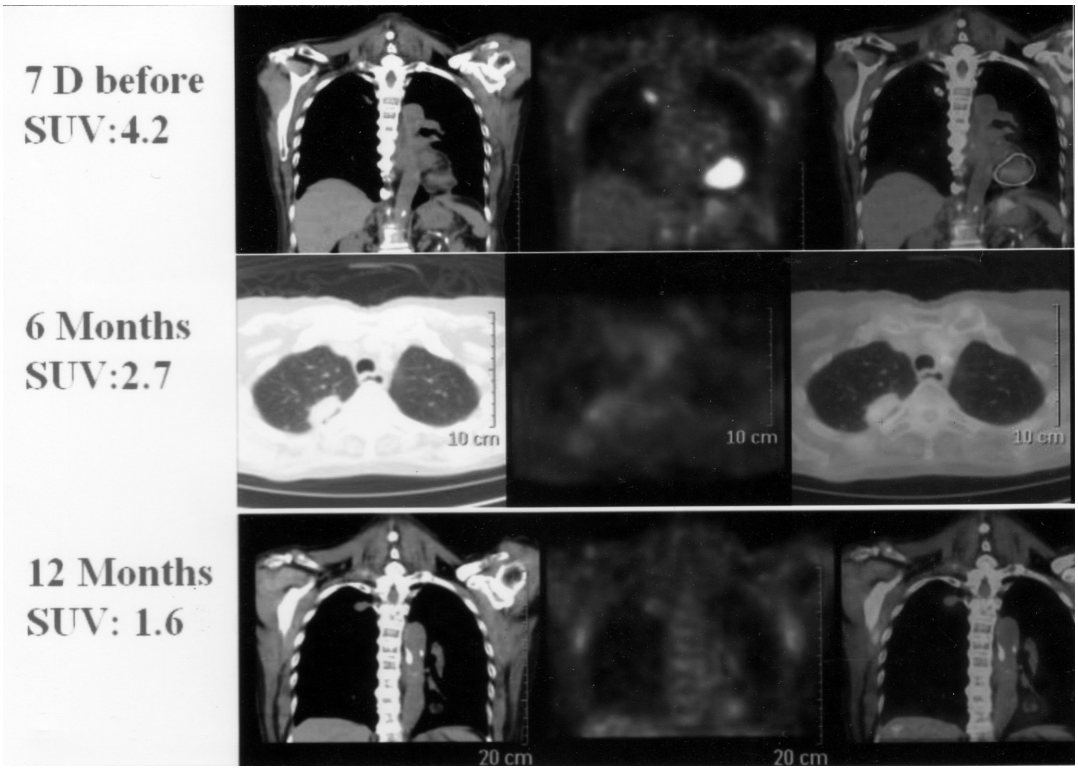

Fig. 3. (A) PET/CT scan before RFA. (B) Six months later. (C) One year later, the SUV has decreased with time.

diction of complete tumor ablation [11]. He reported a minimal GGO margin was significantly associated with tumor recurrence, and a circumferential GGO margin of >5 mm was the minimal margin required to ensure complete tumor ablation. The GGO appeared in our patient and the tumor swelled.

To evaluate and predict treatment response, a CT or PET scan every 3 months is recommended. Enhanced FDG intake, caused by local inflammation, occurs as early as 2-3 days after RFA and can be confused with residual tumor; a PET/CT scab within 2 days of RFA can avoid this ambiguity and will detect incomplete treatment [12]. On the other hand, Yoo [13] found that a PET/CT scan at 6 months correlated better than as early PET/CT (1-4 days) scan in predicting long-term survival. Early imaging results failed to correlate with clinical outcomes at 1 year, so the role of early post-RFA PET/CT scans remains unclear. The standardized uptake value (SUV) positively correlated with tumor size, and a high SUV before RFA indicated a high local recurrence rate. In post-RFA PET/CT scans, an unfavorable uptake pattern (e.g., focal uptake and rim uptake with additional focal uptake on the original tumor) and a progressive increase in SUV after RFA were all related to local recurrence [14]. On the other hand, the SUV value alone was not a reliable indicator, because intense inflammation at the treated site wound increase FDG uptake [15].

The most common RFA-related complication is pneumothorax. The majority of cases are mild and chest-tube insertion occurs in 11-30% of patients. However, pneumothorax can be cat-

astrophic during the procedure. A small pneumothorax will displace and eliminate tension in the visceral pleura, so that the tumor in the lung moves, making the situation in the thoracic cavity unpredictable [3]. Precise insertion of the AP in the tumor then becomes difficult. Hence, adequate patient sedation, and a precise insertion angle and depth of the AP should be planned and followed. Yan *et al*. reported overall morbidity rates in their prospective study comparing 35 initial cases (group 1) and 35 subsequent cases (group 2) receiving RFA [16], and found that the overall rates of pneumothorax detected on a post-procedural CXR were 40% in group 1 and 14% in group 2 (p=0.03). A chest drain was required in 10 patients (29%) with pneumothorax in group 1, compared with 2 (6%) in group 2 (p=0.023). They concluded there is a learning curve for percutaneous lung RFA and predicted a lower morbidity rate could be achieved with more experience [16]. Other complications included pleural effusion, hemoptysis, and subcutaneous emphysema. The morbidity rate was 15.2-55.6% (median, 35.7%) and the mortality rate was 0.4% [17].

Hiraki *et al*. [18] reported their findings in 50 patients with inoperable stage 1 NSCLC who received RFA from 2002-2009. The local progression rate was 30.8% (16/52) and the local control rate was 76.9% (40/52). Median survival was 67 months and mean survival was 59 months. The survival rate at 2, 3 and 5 years was 86%, 74% and 61%, respectively. Local recurrence of tumors at the site of RFA ranged from 3% to 38.1% (median, 11.2%). The median progression-free interval ranged from 15 months to 26.7 months (median, 21 months), and the survival rate at 1, 2 and 3 years was 63-85%, 55-65% and 15-46%, respectively.

Chua *et al*. [19] reported on 148 patients with lung metastases who were prospectively treated with RFA in 2000. Most of the patients had colorectal cancer (108 of 148, 73%). Median overall survival was 51 months and median progression-free survival was 11 months. The 5-year survival rate was 45% which is comparable to pulmonary metastasectomy survival rates. They concluded that RFA for lung metastases achieves long-term survival in nonsurgical candidates with an acceptable complication rate, and hence, supported its incorporation into the oncosurgical management of lung metastases for the purposes of cure, stabilization and disease prolongation. For bilateral lung metastases, Palussiere *et al*. [20] found that 27 out of 67 (40%) patients could be treated with RFA in 1 session, and suggested that 1 session of bilateral lung RFA was safe and effective.

Using RFA for advance-stage NSCLC, Lee *et al*. [21] compared 24 stage III to IV NSCLC patients treated with (1) chemotherapy alone and (2) RFA with chemotherapy from 2000-2004. Median survival times were 29 and 42 months, respectively (p=0.03). They suggested that RFA plays a role as an adjuvant therapy with chemotherapy for patients with stage III to IV lung cancer.

Conclusion

In summary, we reported an early-stage medically inoperable lung cancer patient who received RFA for local control. The therapeutic response of the lung tumor and adjacent lung tissues to the thermal injury was observed. The PET scan showed very good local control 1 year after RFA.

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使用射頻燒灼術（Radiofrequency ablation）治療早期肺癌－一病例報告

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肺癌在台灣的盛行率一直很高。針對早期肺癌的病人，施行手術才有治癒的可能。臨床上因為年紀大、心肺功能差、其他嚴重合併症等，並不是所有早期肺癌的病人都適合接受手術。射頻燒灼術（Radiofrequency ablation, RFA）開始用來治療肝癌，近年來應用在肺部腫瘤的局部控制上，也有預後甚好的結果。我們報告一例老年糖尿病肺功能不佳之早期肺腺癌病人，經過 RFA 治療且追蹤一年後的臨床經驗，同時回顧目前對於 RFA 的資訊。RFA 的侵襲性小，對病人的肺功能影響不大，可以重複施行，且相關的併發症多在可處理的範圍內。影響治療效果最大的因素就是腫瘤的大小，小於三公分的腫瘤治療效果好。治療後的評估多以電腦斷層及正子攝影當作追蹤的工具。*(胸腔醫學 **2013; 28: 102-109**)*

關鍵詞：肺癌，射頻燒灼術（Radiofrequency ablation）

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Granulomatosis with Polyangiitis Initially Presenting with Sinonasal Tumor: A Case Report

Sheng-Chieh Huang*,**, Chih-Feng Chian**, Chen-Hung Chen***, Jih-Ching Li****

Ear, nose and throat involvement is the most common clinical manifestation of granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis, and sinusitis is the most frequent presenting symptom, followed by fever, arthralgia, cough, rhinitis, hemoptysis, otitis, and ocular inflammation. Patients with GPA may present upper respiratory symptoms such as nasal obstruction and epistaxis initially. However, this would lead to a delayed diagnosis and treatment. A 46-year-old man presented with chronic facial pain, numbness, and epistaxis for 3 weeks. Nasal inspection showed an ulcerating tumor in the right osteomeatal complex region. Chest film showed a cavitary mass in the left upper lobe. GPA was confirmed by evidence of necrotizing granulomatous inflammation of nasal tissue and positive cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA). Flare-up of GPA occurred after pulse therapy with high-dose corticosteroid followed by low-dose steroid; anti-CD 20 target therapy with rituximab combined with pulse therapy was then prescribed as an alternative initial induction therapy, followed by low-dose steroid plus hydroxychloroquine. Mycophenolate mofetil as maintenance therapy controlled the progression of GPA and led to remission of the facial and nasal symptoms and the lung mass 3 months after diagnosis of GPA. ***(Thorac Med 2013; 28: 110-117)***

Key words: cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), chronic rhinosinusitis, sinonasal tumor, Wegener's granulomatosis, granulomatosis with polyangiitis (GPA)

Introduction

The Board of Directors of the American College of Rheumatology (ACR), the American Society of Nephrology (ASN), and the European League Against Rheumatism (EULAR) have recommended that the name Wegener's granulo-matosis be changed to granulomatosis with polyangiitis (GPA) [1-3]. "Classic" GPA is a form of systemic vasculitis with necrotizing

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granulomatous inflammation of the upper and lower respiratory tracts, systemic necrotizing vasculitis, and necrotizing glomerulonephritis [1-4]. GPA mostly occurs in older adults. There is no sex predilection and the disease is far more common among Caucasian indi-viduals [5-6].

Patients with GPA usually present with constitutional but nonspecific symptoms, including fever, migratory arthralgia, malaise, anorexia, and weight loss [4-5]. Ear, nose and throat manifestations account for about 90% of symptoms in GPA, and include nasal crusting, sinusitis, otitis media, persistent rhinorrhea, purulent/bloody nasal discharge, and oral and/or nasal ulcers [4-6]. Sinonasal symptoms usually start with rhinitis, epistaxis, and sinusitis [7].

The diagnosis of GPA is established when positive cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) and histopathological evidence of vasculitis with granulomatous inflammation are present in a patient with a compatible clinical presentation, excluding drug-induced vasculitis. Herein, we report a middle-aged man presenting with nasal tumor, nasal obstruction, epistaxis, facial pain and numbness, and a solitary cavitary mass lesion of the left upper lobe. The patient was diagnosed as having GPA by the presence of positive c-ANCA and necrotiz-ing granulomatous inflammation of the nasal tissue. He had a dramatic improve-ment after combined glucocorticosteroid therapy with rituximab as induction therapy, and maintenance therapy with a regimen of oral prednisolone, hy-droxychloroquine, and mycophenolate mofetil.

Case Report

A 46-year-old man visited the ear-nose-throat (ENT) outpatient department (OPD) because of fever of around 38.5°C, myalgia, nasal congestion with epi-staxis, and right facial pain off and on for 3 weeks. Sinoscopy was done, and a swelling mass in the right osteomeatal complex region with easy bleeding at touch was noted. Sinonasal tumor or acute rhinosinusitis could not be excluded. Mag-netic resonance imaging of the paranasal sinuses was then done, and soft tissue plugging of the right osteomeatal complex in the sinonasal cavity, along with dif-fuse mucoperiosteum of the right maxillary antrum with total opacification by re-tention of obstructed excretions and minimal fluid collection in the left maxillary antrum were noted (Figure 1). Admission was recommended, and

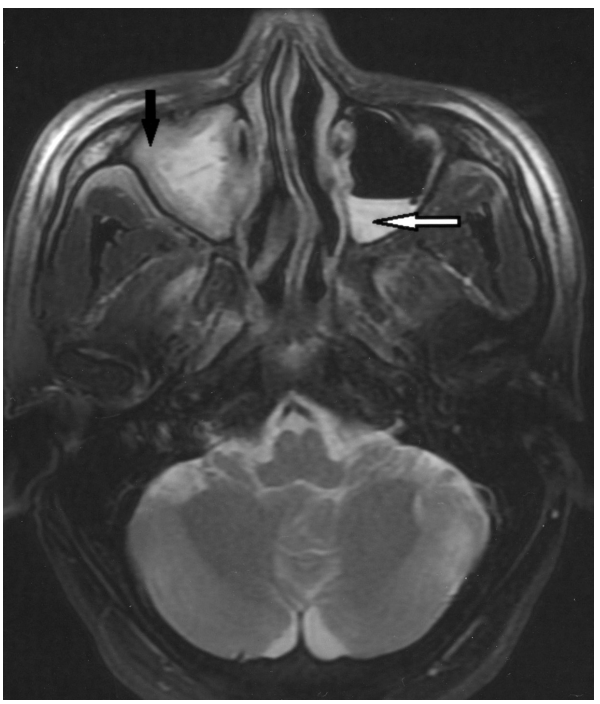

Fig. 1. Magnetic resonance image of paranasal sinuses showed soft tissue plug-ging of the right osteomeatal unit in the sinonasal cavity (black arrow), along with diffuse mucoperiosteum of the right maxillary antrum with total opacification by retention of obstructed excretions and minimal fluid collection in the left maxillary antrum (white arrow).

he was then admitted to our ENT ward for further evaluation.

He was a cigarette smoker, at 1 pack/day for at least 20 years, and he denied any systemic disorders in the past. On arrival, physical examination showed fever of around 38.5°C, mild tachycardia with a pulse rate around 90-100/min, and mild dyspnea with a respiratory rate of 20/min, There was no rales on auscultation or dullness on percussion, and no local tenderness of the abdomen, but numbness and swelling of the right face without motor function impairment was present. Laboratory testing revealed the following: white blood count: 18.06 × 10^6/L; he-moglobin: 12.4 g/dL; platelet count: 411 × 10^6/L; neutrophil: 78.4%; lymphocyte: 11.8%; monocyte: 4.7%; eosinophil: 4.9%. Biochemistry results, including blood urea nitrogen (BUN), creatinine, and aspartate aminotransferase (AST), were in the normal range. Elevation of C-reactive protein (12.3 mg/dL) and the erythro-cyte sedimentation rate (85 mm/hr) were noted. Chest X-ray revealed a cavitary mass in the left apical lung zone (Figure 2).

During hospitalization, fever persisted despite the use of antibiotics. Computed tomography of the chest showed a large mass (size: 7.1 × 5.7 cm) with a cavitary component in the left apical lung zone (Figure 3).

Bacterial culture, acid-fast smear, and fungus culture of sputum and blood cryptococcal antigen were negative. Biopsy of paranasal sinus tissue revealed chronic inflammation with focal palisading granulomatous inflammation and cen-tral necrosis (Figure 4). Acid-fast smear, mycobacterial culture, Gram's stain, bacterial culture, and fungus culture of biopsied nasal sinus tissue were negative. Serum tumor markers including alpha-fetoprotein, carcinoembryonic antigen, CA-199, and anti-squamous cell carcinoma (anti-SCC) levels were in normal ranges. Due to necrotizing granulomatous inflammation in the blood vessel wall of the nasal tissue, autoimmune vasculitis could not be excluded. Normal levels of anti-nuclear antibody and rheumatoid factor were noted. Elevation of serum c- ANCA (6.5 IU/ml) was detected. Under the diagnosis of Wegener's granulomatosis (GPA), the patient was transferred to a chest

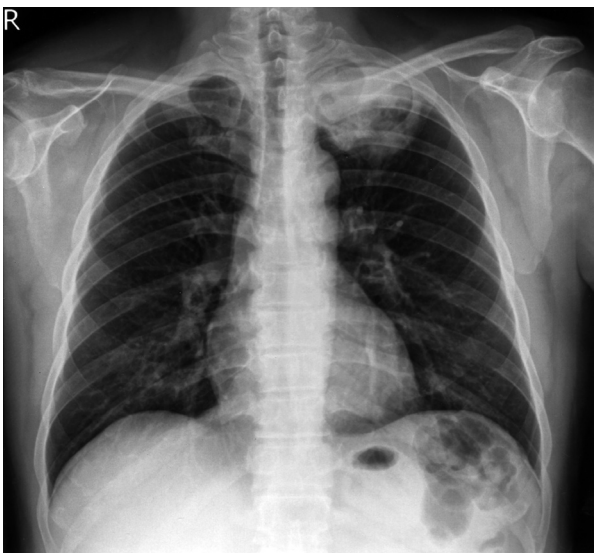

Fig. 2. A cavitary mass in the left apical lung zone.

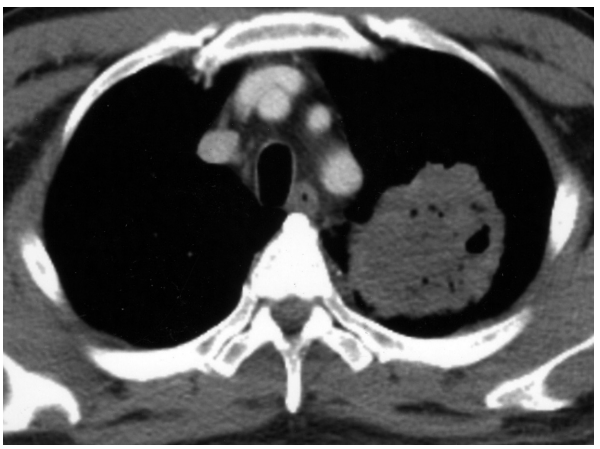

Fig. 3. A large mass (size: 7.1 × 5.7 cm) with heterogeneous and cavitary components in the left apical lung zone.

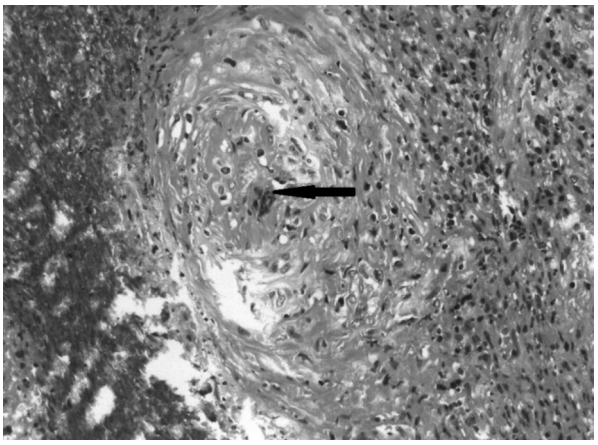

Fig. 4. High power field reveals focal necrosis and granulomatous inflammation in the blood vessel wall (black arrow, hematoxylin & eosin stain, 400X).

specialist.

After discussing treatment with the patient, he decided against a cyclophospha-mide regimen due to the potential side effects such as alopecia and a slight risk of developing blood cancer, such as leukemia or myelodysplasia. Prior to immuno-suppressant therapy, hepatitis B surface antigen, hepatitis A antibody and hepatitis C antibody were all negative. Pulse therapy with intravenous methylprednisolone 500 mg was administered for 3 days; the fever subsided dramatically on the day after completing pulse therapy. Prednisolone 5 mg po bid and azathioprine 50 mg po qd were prescribed after pulse therapy, but azathioprine was discontinued due to markedly elevated liver function and diarrhea. Liver function improved after discontinuation of azathioprine. No architectural abnormality was found in the abdominal sonogram, and viral tests, including cytomegalovirus (CMV), Ep-stein-Barr virus (EBV), herpes simplex virus (HSV) and immunoglobulin M, were negative. Anti-mitochondrial antibody was also negative. Oral daily hy-droxychloroquine 200 mg was also added after pulse therapy, as was oral metho-trexate 7.5 mg weekly. After discharge, he continued oral hydroxychloroquine 200 mg po qd, and prednisolone 15 mg po bid for 3 weeks. However, facial numbness, tearing, and significant eyeball congestion disturbed him again, so he was read-mitted to the Rheumatology, Immunology, and Allergy (RIA) ward, where facial numbness and eyeball congestion improved after targeted therapy with intravenous MabThera (rituximab) 1000 mg, followed by pulse therapy with methylprednisolone 500 mg. Prednisolone was tapered gradually at the outpatient department (OPD). After discharge, he presented to the chest OPD due to inter-mittent coughing up of blood-tinged material for 1 month. The second course of target therapy with rituximab followed by pulse therapy was performed 3 weeks after the first course.

Intermittent facial pain and numbness bothered him, so mycophenolate mofetil 250 mg po bid was added for maintenance therapy after the second course of tar-geted therapy. The facial pain and numbness subsided, and oral prednisolone was tapered gradually to 10 mg daily as maintenance therapy. Follow-up chest X-ray 3 months after medical treatment showed regression of the left upper opacity.

Discussion

Acute sinonasal symptoms of GPA are commonly misdiagnosed as infectious or allergic in etiology, but the addition of the lung mass seen in our patient gave us a hint that the sinonasal symptoms may be the tip of the iceberg. As we found in this case, a multidisciplinary team evaluation may facilitate confirmation of the diagnosis of GPA.

Granulomatosis in the lung may be angiocentric or bronchocentric in distribu-tion. GPA

is of an angiocentric form [8]. GPA can be classified into renal and non-renal patterns [9]. Hematuria (microscopic or macroscopic) and proteinuria are seen in renal GPA, but not in non-renal GPA [9]. Necrotizing glomerulonephritis is absent in non-renal GPA [8]. Non-renal GPA has less cutaneous and pulmonary involvement than renal GPA, but more otorhinolaryngological involvement, and the disease pattern may change to involve the kidney [9], so long-term follow-up of such patients is essential.

Chronic rhinosinus involvement in GPA can lead to nasal perforation, saddle nose deformity, serous otitis, and hearing loss [7,10], so refractory chronic rhi-nosinusitis should be evaluated more carefully and more aggressively if symptoms of sinus pain, nasal obstruction, and purulent/bloody nasal discharge develop, as in our patient. Nasal biopsy, although relatively noninvasive, is limited by the small amount of tissue that can be removed. Repeated nasal biopsy may be indicated if progressive sinonasal manifestations develop [10]. Our patient underwent functional endoscopic sinus surgery with sinus biopsy, and the histopathological exam demonstrated necrotizing granulomatous inflammation. Therefore, both an infectious process and vasculitis should be put into the differential diagnosis, and a negative tissue bacterial culture, fungus culture, and mycobacterial culture ex-cluded the infectious process.

Routine laboratory tests, including complete blood count with differential, plasma creatinine, and urinalysis should be obtained from all patients with sus-pected, but nonspecific, GPA. A serologic ANCA test is indicated for a suspicion of GPA. Approximately 82-90% of patients with GPA are ANCA positive, depending on the severity of disease [11-12]. The clinical use of c-ANCA as a diag-nostic marker for GPA was confirmed in a large prospective European study, with a sensitivity of 60% and a specificity of 95%.

An abnormality of the paranasal sinuses observed in sinonasal computed to-mography may demonstrate mucosal thickening, subtotal opacification, bony de-struction, sclerosing osteitis, or bony thickening [13]. Our patient with GPA demonstrated a nasal tumor with nasal obstruction complicated by progressive chronic rhinosinusitis with subtotal opacification of the right maxillary sinus, along with diffuse mucoperiosteum due to the granulomatous component. We did not perform biopsy of the lung mass, but did perform nasal biopsy, which was safe with relatively less risk and easier to perform than CT-guided biopsy of the lung lesion. Fortunately, the nasal biopsy combined with positive serum ANCA and the lung lesion demonstrated by chest image provided a definite diagnosis of GPA.

The cavitary mass in the left upper lobe presented by our patient was identified accidently while seeking to detect the possible source of the infection or inflam-matory process. Involvement of the airway or pulmonary parenchyma in GPA may present hemoptysis, dyspnea and pleuritic pain [6,14]. The most commonly reported chest radiograph findings were nodules (20-90%) and patchy or diffused opacities (20-50%) [14-17]. Approximately 30-50% of nodules are cavitary [14]. Cavitation can occur in benign and malignant solitary pulmonary nodules [18], and with infection, vasculitis, primary lung cancer, and metastatic disease. Irregularity of the inner cavity wall was significantly more frequent in malignancy [19]. A lung nodule in an upper lobe location increases the possibility that a lesion is lung cancer [20]. As with our patient with a cavitary mass in the left upper lobe,

malignancy must be ruled out first. We searched the Medline database by cross-searching between malignancy and GPA, and only a few case reports were found; there was no patient with GPA combined with lung cancer, but one GPA patient with bladder cancer was found. After establishing the diagnosis of GPA, the lung mass regressed with immunosuppressant therapy, and biopsy of the lung mass was avoided.

Cyclophosphamide combined with corticosteroid remains a "gold standard" regimen in the treatment of GPA [21]. In 2 randomized trials, rituximab was as effective as cyclophosphamide in inducing remission among patients with newly diagnosed or relapsed GPA [17,22]. So patients who have a contraindication to cyclophosphamide therapy or refuse such therapy may choose rituximab as an al-ternative therapy, as seen in our case.

In conclusion, a patient with refractory upper respiratory tract abnormalities combined with fever should be carefully approached; care and evaluation by a multidisciplinary team may be helpful in shortening the interval to diagnosis. We recommend that GPA should be put into the differential diagnosis of any patient presenting with sinonasal symptoms in addition to fever and a lung parenchymal abnormality in the chest X-ray.

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以鼻竇腫瘤爲最初表現的肉芽腫併多發性血管炎：病例報告

黃聖傑 *,** 簡志峰 ** 陳政宏 *** 李日清 ****

韋格納氏肉芽腫（Wegener's granulomatosis）於 2011 年 1 月被三家學會建議更名為肉芽腫併多發性血管炎（granulomatosis with polyangiitis）。耳鼻及喉部侵犯是最常見的臨床表現，副鼻竇炎是很常見的症狀，緊接著是發燒、關節痛、咳嗽、鼻炎、咳血、耳炎及眼球發炎。此類病人初期可能僅表現上呼吸道症狀，例如鼻腔阻塞、流鼻血，所以可能造成延遲診斷及治療。我們提出的一個 46 歲中年男性因起初以慢性臉部疼痛及麻與流鼻血持續約 3 週，被發現有右鼻竇腫瘤。胸腔 X 光檢查呈現左上肺葉開洞腫塊。這個病人的診斷是由右側鼻病灶病理切片呈現壞死性肉芽腫，及陽性抗嗜中性白血球細胞質抗體確立診斷。病人在脈衝式療法（pulse therapy with high dose corticosteroid）後又再度復發，選擇標靶治療藥物 rituximab（anti-CD 20）當作替代式療法，接著使用低劑量類固醇併 hydrochloroquine 及 mycophenolate mofetil 當作維持性療法（maintenance therapy），且經過三個月後，上呼吸道及臉部症狀改善且左上葉開洞病灶也幾乎消失。*(胸腔醫學 **2013; 28: 110-117**)*

關鍵詞：抗嗜中性白血球細胞質抗體，慢性鼻竇炎，鼻竇腫瘤，韋格納氏肉芽腫，肉芽腫併多發性血管炎

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Tracheal Papilloma Presenting as Refractory Asthma: A Case Report

Ching-Yao Yang, Jann-Yuan Wang

Recurrent respiratory papillomatosis (RRP) is a benign neoplasm in the respiratory tract that is recurrent in nature and caused by human papilloma virus (HPV) infection. RRP may arise from anywhere in the respiratory tract, but solitary tracheal papilloma is a relatively rare form of RRP and is frequently misdiagnosed as asthma due to the similar symptoms, including cough, dyspnea, and wheezes. We report a 25-year-old man with tracheal papilloma that was diagnosed as asthma initially. His dyspnea and wheezes were refractory to bronchodilators and inhaled corticosteroids. Chest computed tomography (CT) disclosed a cauliflower-like tumor in the trachea with nearly total obstruction. Surgical resection of the tumor was performed with the support of extracorporeal membrane oxygenation (ECMO), and the pathology report indicated squamous papilloma. HPV type 72 was detected in the tumor tissue by polymerase chain reaction (PCR) followed by a HPV genotype-specific hybridization method. We concluded that a thorough evaluation should be carried out if the asthma is difficult to control. ECMO may be helpful for tracheal tumor resection in patients for whom a conventional anesthesia technique is unsafe. ***(Thorac Med 2013; 28: 118-124)***

Key words: tracheal papilloma, recurrent respiratory papillomatosis, refractory asthma, extracorporeal membrane oxygenation, human papilloma virus

Introduction

Recurrent respiratory papillomatosis (RRP) is a benign neoplasm in the respiratory tract and has a recurrent nature. It is caused mainly by human papilloma virus (HPV) infection [1]. The incidence ranges from 4 to 12 cases per 1,000,000 person-years, indicating that RRP is a quite rare disease [2]. The papilloma may arise from anywhere along the respiratory tract, but the most commonly involved site is the laryngeal area [3]. Solitary tracheal papilloma without laryngeal involvement is a relatively rare form of RRP [3] and is usually manifested by cough, wheezes, and dyspnea [4]. Due to the nonspecific symptoms and unremarkable findings in chest radiography, patients with tracheal papilloma are easily misdiagnosed as having asthma, bronchitis, or pneumonia. Herein, we report the case of a 25-year-old man with tracheal papilloma that was diagnosed as refractory asthma initially.

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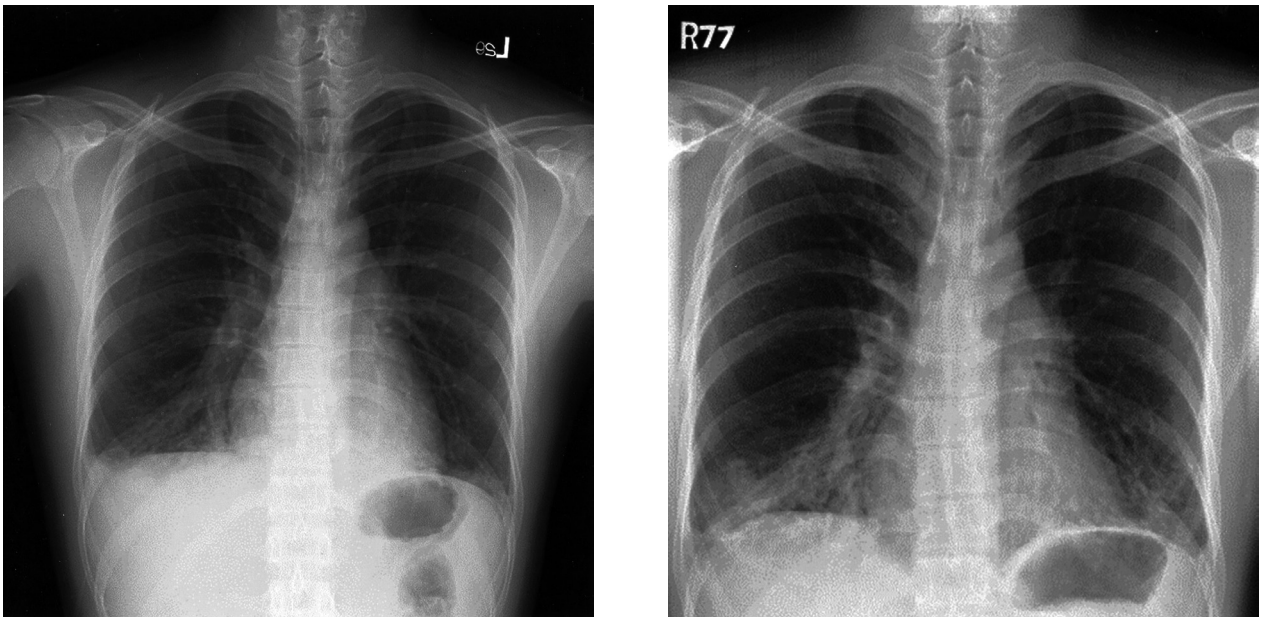


(A) (B)

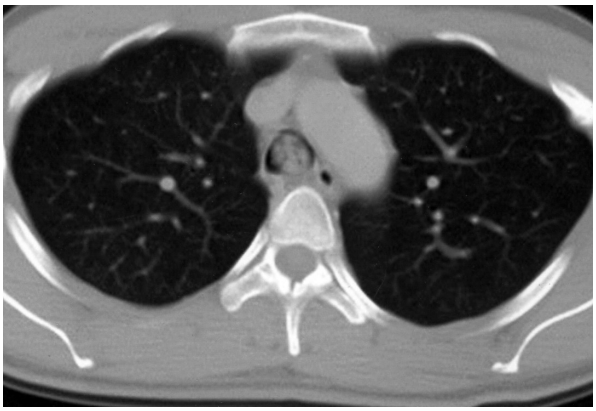
Fig. 1. Chest radiography of tracheal papilloma. (A) The film taken in the outpatient department showed increased bilateral lower lung infiltrates and a faint opacity in the lower trachea. (B) The film taken 2 weeks later showed a more prominent tracheal opacity.

Case Report

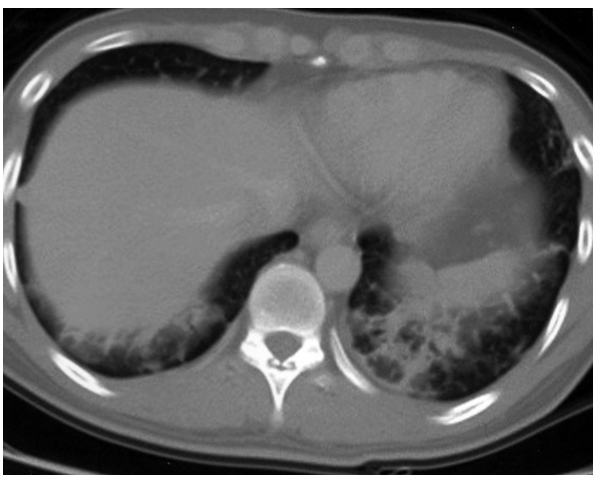
This 25-year-old man denied cigarette smoking and had no systemic disease. He had suffered from dry cough and exertional dyspnea for 3 months and visited our hospital in February 2009. Asthma was suspected initially because auscultation of the lungs revealed bilateral end-expiratory polyphonic wheezes. He used short-acting bronchodilators and inhaled corticosteroids during the subsequent 2 weeks, but his symptoms did not improve. Chest radiography (Figure 1A) showed increased bilateral lower lung infiltrates and a very faint opacity in the trachea, which was almost invisible and neglected at his first visit to our hospital. Because of persistent wheezes and lower lung infiltrates, and a suspicion of refractory asthma and pneumonia, he was admitted and treated with systemic steroids and antibiotics.

However, his dyspnea aggravated soon after and he required oxygen support through a Venturi mask. Follow-up chest radiography (Figure 1B) revealed a faint tracheal lesion, which was slightly more prominent than in the film taken 2 weeks prior to this, and more prominent lower lung consolidation. Computed tomography (CT) of the chest yielded a cauliflower-like, wide-based mass protruding from the posterior wall in the lower trachea (Figure 2A), with nearly total obstruction and bilateral lower lung consolidations (Figure 2B). Because of the critical airway and difficulty in ventilation during the procedure, interventional bronchoscopy for the tracheal tumor was not done. Tumor resection was then performed through sternotomy with venovenous ECMO support.

A whitish, papillomatous tumor about 4 cm above the carina arising from the posterior wall of the trachea was found intraoperatively

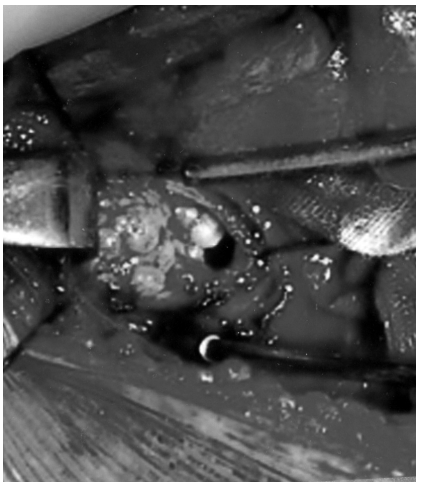


(A)

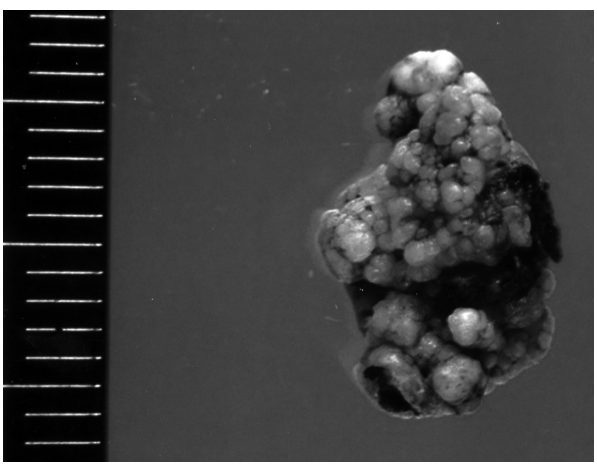


(B)

Fig. 2. Computed tomography of chest with contrast enhancement. (A) A cauliflower-like, wide-based mass protruding from the posterior wall in the lower trachea. (B) Bilateral lower lung consolidations



(A)



(B)

Fig. 3. Intraoperative imaging and gross picture of resected papilloma (A) Through sternotomy and incision of the anterior tracheal wall, a whitish, polipoid mass was disclosed with nearly total obstruction of the airway. (B) The 2.6 × 1.8 × 1.8 cm polypoid whitish mass had an irregular surface and firm texture.

(Figure 3A). The tumor was resected, followed by anastomosis of the incised trachea. ECMO support was shifted to endotracheal tube ventilation after operation, and extubation was performed within 1 day. The postoperative course was uneventful, and the patient was discharged 2 weeks after operation. About 3 months later, he underwent a bronchoscopy survey and no recurrence of the tracheal papilloma was found.

The resected tumor was a 2.6 × 1.8 × 1.8 cm polypoid whitish mass in gross appearance (Figure 3B) with an irregular surface and firm texture. On microscopic examination, the tumor consisted of numerous papillomatous fronds lined by hyperplastic, squamous epithelium showing moderate parakeratosis and hyperkeratosis (Figure 4). The tumor was diagnosed as a solitary squamous papilloma, and the section margin was free from papilloma cells. We used a modified MY11/GP6+ PCR for HPV DNA

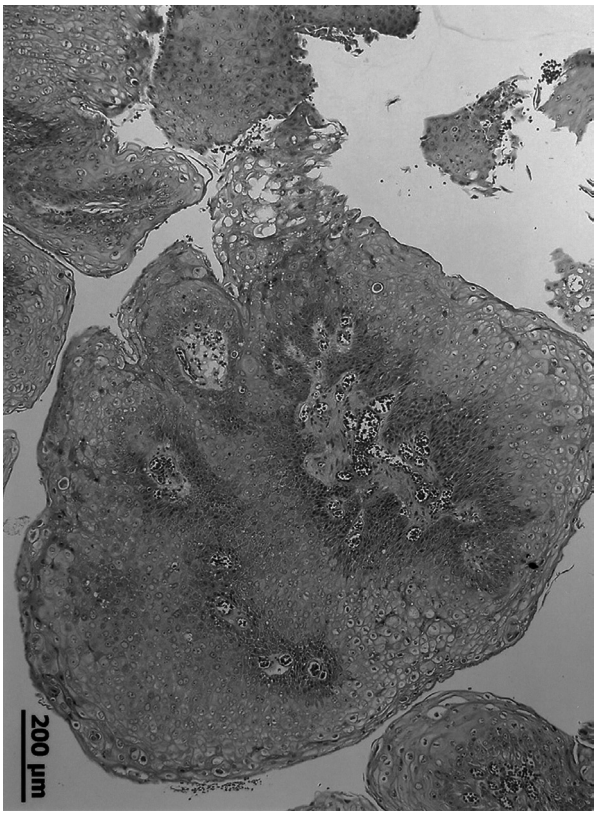


Fig. 4. Hematoxylin and eosin stain of the papilloma, 200X. The tumor consisted of numerous papillomatous fronds lined with hyperplastic squamous epithelium showing moderate parakeratosis and hyperkeratosis.

amplification, followed by HPV genotype-specific hybridization with a gene chip [5] to identify HPV deoxyribonucleic acid (DNA) in the papilloma tissue. HPV type 72, a rare genotype with a low risk of malignant transformation, was detected.

Discussion

RRP, characterized by its recurrent nature, presents a variable and prolonged course despite treatment. It has been classified into juvenile-onset and adult-onset types based on the onset age (cut-off: 13 years old) [6]. The juvenile-onset form is more frequent and has a more aggressive clinical course than the adult-onset form [6]. RRP involves the larynx, and solitary tracheal papilloma is an infrequent entity. In a case series including 244 RRP patients, only 3 (1.2%) had an isolated tracheal papilloma without laryngeal involvement, and 26 (10.6%) had both laryngeal and tracheal papillomatosis [3]. In another large series study, only 40 (8.9%) out of 448 RRP patients had lower airway papillomatosis, including tracheal, bronchial, and pulmonary types [7]. Because of the different locations, the presentation and prognosis of laryngeal papilloma and tracheal papilloma are quite different. Lower airway papillomatosis was reported to present a more aggressive course than laryngeal papillomatosis. Risk factors for RRP to spread to the lower respiratory tract included infection by HPV type 11, age below 3 years, and tracheostomy performed to avoid airway obstruction [7].

HPV is generally accepted as the cause of RRP. HPV infects primarily keratinocytes through microtrauma or abrasions on the surface of the epithelium. By suppressing effective TH1-like immune responses to HPV, this virus induces a tumorigenic microenvironment, and alters the expression of genes regulating cellular growth and the differentiation that favors the disordered proliferation of infected host cells and the development of RRP [8]. HPV is divided to low- and high-risk groups based on the risk of malignant transformation to cervical cancer. The low-risk group includes HPV types 6, 11, 40, 42, 43, 53, 54, 61, 72, 73, and 81. HPV types 6 and 11 are the most common genotypes in association with RRP [1]. HPV types 16 and 18 are the most common genotypes of high-risk groups frequently associated with severe atypical and invasive carcinoma in the uterine cervical epithelium [9]. The as-

sociation of these high-risk HPV types with malignant transformation in RRP is in doubt. HPV DNA in the papilloma tissue was detected in 45 of 51 patients, including HPV type 6 in 19 (42%), HPV type 11 in 13 (29%), HPV type 16 in 5 (11.1%), and HPV type 18 in 1 (2.2%) [10]. There was no correlation between HPV type and adult- or juvenile-onset RRP. The papilloma in these patients finally progressed to squamous cell carcinoma in 4 patients, including 2 with HPV type 6, and one each with HPV type 16 and HPV type 6 and 18 co-infection. HPV type 72, found in our case, is a rare genotype and has never been reported in the literature in association with tracheal papilloma.

The diagnosis of tracheal papilloma by bronchoscopic biopsy is quite straightforward if the tracheal tumor is disclosed on the chest image. Multiple cauliflower-like neoplasms with a smooth and neat surface and without necrosis can be seen on endoscopy. The wheezes heard from our patient were polyphonic, not monophonic. This might be due to the irregular surfaces of the papilloma, which produce multiple narrowing of the airway. During bronchoscopy, these neoplasms easily bleed when touched because of their fragile nature. After the definite diagnosis, the treatment goals of RRP mainly include curing the lesions and preventing recurrence. The recurrent nature of RRP necessitates repeated treatments, and the interval between treatments varies from 2 weeks to 72 months [7]. A case of tracheal papilloma with an exceptionally long interval of 21 years between recurrences has been reported [10]. Surgical removal during endoscopy is still the fundamental treatment, and the most extensively used approaches in recent years are laser ablation and microdebrider removal. Other available approaches include electrocautery and cryotherapy, but there is currently no study that demonstrates the superiority of any 1 modality over the others. However, interventional bronchoscopy under endotracheal intubation may not be feasible if the obstruction is too severe to maintain adequate ventilation. The cases of 2 patients with tracheal papilloma that underwent tumor resection with ECMO support have been reported [11]. ECMO is likely to be the safest option for tracheal surgery in high-risk patients.

Conclusion

Though tracheal tumor is a rare condition in patients presenting polyphonic wheezes and dyspnea, the tumor may have quite non-specific symptoms and unremarkable imaging that leads to a delayed diagnosis. We reported herein a case of tracheal papilloma mimicking refractory asthma with nearly total airway obstruction. A rare genotype of HPV, type 72, was also identified, though the risk of malignant transformation in RRP is still uncertain. Subsequent follow-up is required for early detection and treatment of recurrence.

Acknowledgments

The genome analysis was performed at the Center of Genomic Medicine of National Taiwan University Hospital.

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以頑固型氣喘爲表現的氣管內乳突瘤：案例報告

楊景堯　王振源

反覆性呼吸道乳突瘤（Recurrent respiratory papillomatosis, RRP）為人類乳突病毒所造成的一種呼吸道良性腫瘤，有反覆發作難以根治的特性。RRP 可發生在呼吸道的任何地方，但以喉部為最常見，單獨發生在氣管而無其他部位侵犯者較為稀少。因為臨床症狀如喘及嘯鳴聲等不具特異性，而胸部 X 光對於氣管內病灶又較不敏感，氣管內乳突瘤往往難以早期診斷而被誤診為氣喘或其他阻塞性呼吸道疾病。此處我們報導一位罹患氣管乳突瘤的 25 歲男性，起初因咳嗽、喘及嘯鳴聲等徵候被診斷為氣喘，但在支氣管擴張劑及吸入性類固醇的治療下其症狀仍不斷惡化。胸部電腦斷層顯示在氣管內有一花椰菜狀的腫瘤，造成氣管幾乎完全阻塞。由於傳統的氣管插管無法在手術中達到足夠的換氣，此病人在葉克膜體外循環機的支持下順利接受了氣管內的乳突瘤切除。利用原位雜交聚合體鍊狀反應，我們發現在乳突瘤組織裡偵測到一少見的人類乳突病毒基因型（第 72 型）。由此案例可知，當氣喘對傳統治療反應不佳時，需考慮其他阻塞型呼吸道疾病，氣管腫瘤雖然少見仍須列入考慮。在呼吸道腫瘤的手術中如遇到換氣困難的情況，葉克膜體外循環機為一安全的方式來維持術中適當的通氣使手術得以順利進行。*(胸腔醫學 **2013; 28: 118-124**)*

關鍵詞：氣管乳突瘤，反覆性呼吸道乳突瘤，頑固型氣喘，葉克膜體外循環機，人類乳突病毒

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Pulmonary Angiosarcoma Presenting as Bilateral Pulmonary Nodules and Pericardial Effusion – A Case Report

Hung-Jen Fan, Hao-Chien Wang, Chong-Jen Yu

Angiosarcomas are primary vascular malignancies with a highly invasive character. The lung is the most common site of metastasis, but primary pulmonary angiosarcomas are rarely reported. We reported a case of suspicious primary pulmonary angiosarcoma with the initial presentation of bilateral lung nodules and pericardial effusion. Diagnosis was made by surgical biopsy via thoracoscopy. The clinical characteristics, histopathologic features and treatment options were also reviewed in this article. ***(Thorac Med 2013; 28: 125-130)***

Key words: angiosarcoma, pulmonary angiosarcoma, primary intrathoracic sarcoma

Introduction

Angiosarcoma is a rare malignant tumor derived from endothelial cells of vascular or lymphatic origin. It accounts for less than 1% of all kinds of sarcoma, and has nearly the worst prognosis of this tumor group [1]. Since the vascular and lymphatic drainage spreads to all the organs, angiosarcoma can involve any region of the body. Skin and soft tissue are the most common sites of involvement [2]. Hemoptysis is the most frequent presentation when angiosarcoma occurs in the lung. Early diagnosis is difficult since more than 50% of patients may only have non-specific respiratory symptoms [3]. Herein, we describe a case of angiosarcoma presenting with bilateral pulmonary nodules and pericardial effusion, followed by rapid disease progression and brain metastasis.

Case Report

A 54-year-old man presented in October 2010 with orthopnea and dyspnea on exertion that had lasted for 4 months. Two weeks before coming to our hospital, he had productive cough and hemoptysis. Body weight loss of around 4 kg within 6 months was noted by the patient. There was no fever, chest tightness, palpitation or sudden consciousness change. He was relatively healthy, but had a smoking habit of less than 1 pack-per-day for 30 years. He had worked in a bank since his 20s. He denied a history of contact with animals or sick people. No toxin exposure could be clearly identified. The chest X-ray revealed bilateral

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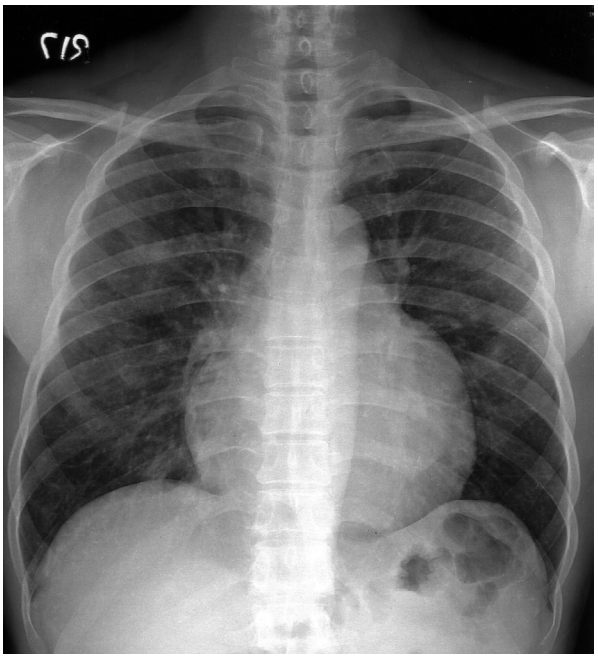
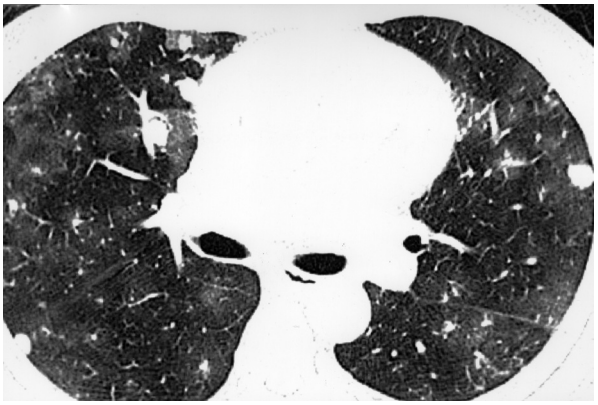


(A)

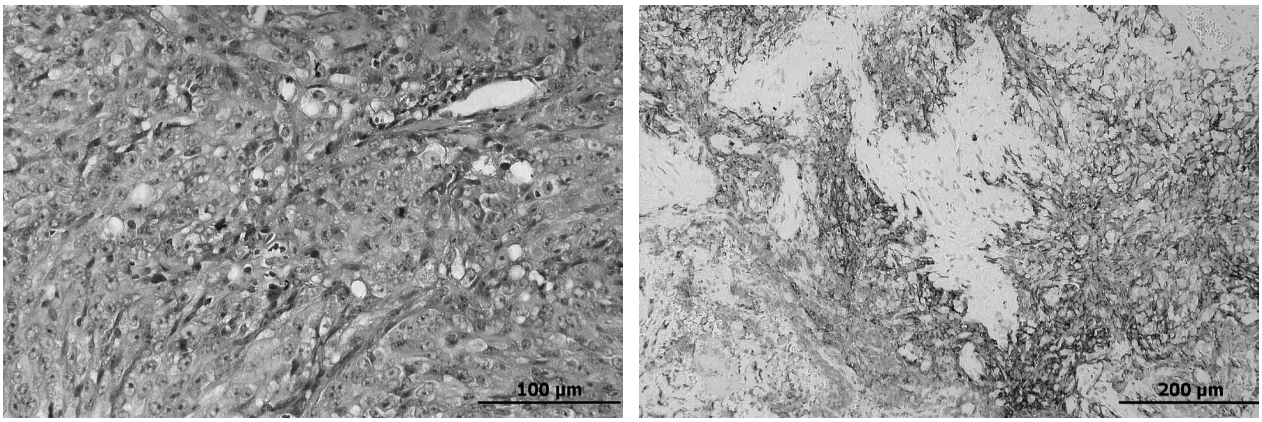


(B)

Fig. 1. (A) Chest X-ray. Bilateral nodular lesion and ill-defined consolidation. (B) Chest CT scan. Bilateral lung nodules.

lung nodules with an ill-defined consolidation patch and increased cardiothoracic ratio (Figure 1A). Chest computed tomography (CT) scan disclosed multiple nodules with surrounding ground-glass opacity (Figure 1B), tiny mediastinal lymphadenopathies, and evenly distributed pericardial effusion without loculation. Both cytology examination and acid-fast stain of the sputum showed negative results. Cardiac sonography revealed a large amount of pericardial effusion, but no pericardial nodularity or thickening of the chamber walls. He then underwent a thoracoscopic pericardiectomy. A 6 × 6 cm piece of thickened pericardium was obtained and a pericardio-pleural window was created simultaneously. The pericardial effusion was serosanguineous in character, with total nuclear cells of 800/μl composed mainly of mesothelial cells and histiocytes. Cytology examination was negative. Histological examination of the pericardium revealed fibrous tissue and focal chronic inflammation without malignant cells. Cultures of all specimens yielded no specific pathogens. The patient's symptoms of dyspnea and orthopnea were relieved after surgery. He refused any further invasive procedure to approach the pulmonary lesions. Because of the pericarditis with an unknown cause, and possible tuberculosis infection in an endemic area, he started on standard anti-tuberculosis agents.

Two months later, the patient was hospitalized again for massive hemoptysis during exercise. During this period, he had had occasional dizziness, progressive general malaise and dyspnea on exertion. Repeat chest CT scan showed enlarging bilateral lung nodules, pericardial nodularity and a soft tissue lesion surrounding the distal superior vena cava, with right atrium invasion. Brain CT showed 2 enhancing nodules at the left high frontal lobe and right parietal lobe with perifocal edema, compatible with metastatic brain lesions. Biopsy of the lung nodules via both an echo-guided procedure and bronchoscopy showed granulation tissue only. He then underwent video-assisted thoracoscopic surgery for right middle lobe wedge resection. Intraoperative findings included cyanotic and sclerosing change in the lung paren-



(A) (B)

Fig. 2. Microscopic examination of thoracoscopic surgery specimen and immunohistochemical stain. (A) Vascular thrombus with tumor cells containing hyperchromatic spindled nuclei and eosinophilic cytoplasm. (B) Tumor cells are positive for CD31.

chyma and adhesion of the right upper lobe and middle lobe to the chest wall. The microscopic examination showed extensive small and large vascular tumor thrombi and multiple pulmonary tumor deposits. The tumor cells contained hyperchromatic spindled nuclei and eosinophilic cytoplasm (Figure 2A). Immunohistochemical staining showed the cells were positive for CD31 (Figure 2B) and vimentin, but negative for cytokeratin, S100, SMA, HMB45 and FB. On the basis of these findings, a diagnosis of angiosarcoma involving the lung, brain and pericardium was made. The patient then underwent chemotherapy with liposomal doxorubicin 60 mg every 3 weeks. The tumors responded to the initial treatment in the first 3 cycles. However, chest CT scan after the 5th cycle of liposomal doxorubicin revealed pulmonary nodules increasing in size and number. The chemotherapy regimen was shifted to paclitaxel 120 mg per week, but the patient's treatment course was complicated by hospital-acquired pneumonia and life-threatening hemoptysis. Despite intensive management and life support, the patient died of respiratory failure in May 2011.

Discussion

Angiosarcomas typically affect middle-aged adults, with a male-to-female ratio of around 3:1 [1]. These tumors can be further subdivided into cutaneous angiosarcoma, lymphoedema-associated angiosarcoma, radiation-induced angiosarcoma, primary breast angiosarcoma and soft tissue sarcoma, based on the different primary sites and associated conditions [4]. The cutaneous form occasionally develops in elderly white men, presenting particularly as scalp or head and neck tumors, while the soft tissue form may arise in any visceral organ. Several risk factors related to angiosarcoma have been described. Chronic lymphoedema is the most established predisposing defect. As an adjuvant treatment for localized malignancy, radiotherapy is also an independent risk factor for soft tissue sarcomas, especially angiosarcomas [5]. Breast angiosarcoma is deemed to be a specific subgroup due to the complicated nature of its

cause. Lymphoedema is a common complication with primary breast cancer, due to either tumor infiltration or debulking surgery. Radiotherapy is also performed as standard treatment for advanced breast cancer. Even mutations in the DNA repair genes related to breast cancer, like BRCA1 and BRCA2, can predispose to the development of breast angiosarcoma [6]. However, none of the above risk factors could be identified in our patient. Despite insufficient evidence, some epidemiological studies have suggested angiosarcomas can be caused by localized immunodeficiency in patients with acquired immunodeficiency syndrome [7]. The anti-HIV antibody test for our patient yielded negative results.

The hallmark of angiosarcoma morphology is pleomorphic, malignant endothelial cells that can be rounded, polygonal or fusiform in shape. Functional sinusoids, which are composed of abnormal endothelial cells, have normal vascular channels in well-differentiated cases. In poorly-differentiated tumors, the architecture becomes chaotic and the vascular sinusoids dissect between collagen bundles. These pathologic changes result in easy-bleeding, which is the characteristic presentation of angiosarcomas [4]. Immunohistochemical staining can help in diagnosing angiosarcomas, for these tumors generally express useful markers, like von Willebrand factor, CD31, CD34 and vascular endothelial growth factor (VEGF) [8].

Radical surgery with total resection is the treatment of choice for angiosarcoma with a localized lesion. Adjuvant chemotherapy is a reasonable choice because of the highly vascular invasion and ease of hematogeneous spreading, but evidence of effective treatment is lacking. There is currently no treatment guideline for metastatic angiosarcoma. The effect of systemic therapy is frequently limited by rapid disease progression and the complication of hemorrhage. In a retrospective study, 21 patients with advanced angiosarcoma received doxorubicin-based chemotherapy; 13 (64%) of the 21 patients had at least a partial response, but prolongation of overall survival was not provided [9]. The systemic administration of high doses of recombinant interleukin-2 was reported to cause regression of pulmonary angiosarcoma in 1 case [10]. VEGF-A may be consistently expressed at higher concentrations in angiosarcomas than in normal vascular structure. Although the case numbers in 2 studies were small, encouraging responses were achieved with VEGF-A monoclonal antibody, such as vebacizumab. [11-12].

In conclusion, angiosarcomas are tumors of vascular or lymphatic duct origin. Pulmonary angiosaromas are usually non-resectable and are associated with a poor prognosis -- most patients die within 1 year after diagnosis. Effective systemic treatments are still under evaluation.

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以肺部結節及心包膜積水表現的肺部血管肉瘤－病例報告

方泓仁　王鶴健　余忠仁

血管肉瘤是由血管組織原發的惡性腫瘤，具有高度惡性及侵襲性的表現。肺部是最容易發生轉移性血管肉瘤的器官，但原發性的肺部血管肉瘤卻極少被報告。在此我們提出一個疑似原發性肺部血管肉瘤的病例報告，此個案以雙側肺腫瘤及心包膜積水為初始表現，經由胸腔內視鏡手術切片證實。同時在本篇文章中也回顧了關於血管肉瘤的臨床表現、組織病理學特徵及治療的選擇。*(胸腔醫學* ***2013; 28: 125-130)***

關鍵詞：血管肉瘤，肺部血管肉瘤，原發性胸腔內肉瘤

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Huge Solitary Fibrous Tumor of the Pleura – Report of a Case

Chun-Kai Huang, Huey-Dong Wu*, Chong-Jen Yu

Solitary fibrous tumor of the pleura (SFTP) is a rare neoplasm from mesenchymal cells. It is usually asymptomatic and the diagnosis is often delayed; 10-20% of SFTPs are classified as malignant. Benign SFTPs are almost curable with complete surgical resection. Clinical and radiological assessment can provide a hint of SFTP, but is often inadequate for a definitive diagnosis. Although routine fine needle aspiration biopsy (FNAB) is not suggested in SFTP, tissue proof is still necessary if disease management would be substantially affected by the results, or if surgical intervention is contraindicated. Herein, we report a 79-year-old woman with progressive dyspnea and a huge mass in the left lower lung zone. She and her family decided against surgical intervention. She was diagnosed as having SFTP with echo-guided FNAB. ***(Thorac Med 2013; 28: 131-137)***

Key words: solitary fibrous tumor, pleural tumor, prognosis

Introduction

Solitary fibrous tumor of the pleura (SFTP) is a rare neoplasm that accounts for less than 5% of all pleural tumors. Wagner reported the first case of SFTP in 1870, and the pathologic description was mentioned in 1931 [1]. Many terms have been used to describe this neoplasm over the decades (such as localized mesothelioma, localized fibrous mesothelioma, localized benign fibroma, or submesothelial fibroma) due to its unknown origin. Immunohistochemical staining, flow cytometry, and electron microscopic analysis have demonstrated that these neoplasms originated from the submesothelial mesenchymal layer [2]. Most SFTP tumors arise from the visceral pleura, but some arise from the parietal. Solitary fibrous tumors have been described not only in other thoracic areas (mediastinum, pericardium and pulmonary parenchyma), but also in extrathoracic regions (meninges, epiglottis, salivary glands, thyroid, kidneys and breast) [3]. Approximately 800 cases of SFTP were reported in the literature during the period between 1931 and 2002, and 760 additional cases of SFTP were reported between 2004 and 2011 [4]. The increase in the occurrence of SFTP might be due to advances in the methods of diagnosis, especially with the assistance of immunohistochemistry and the

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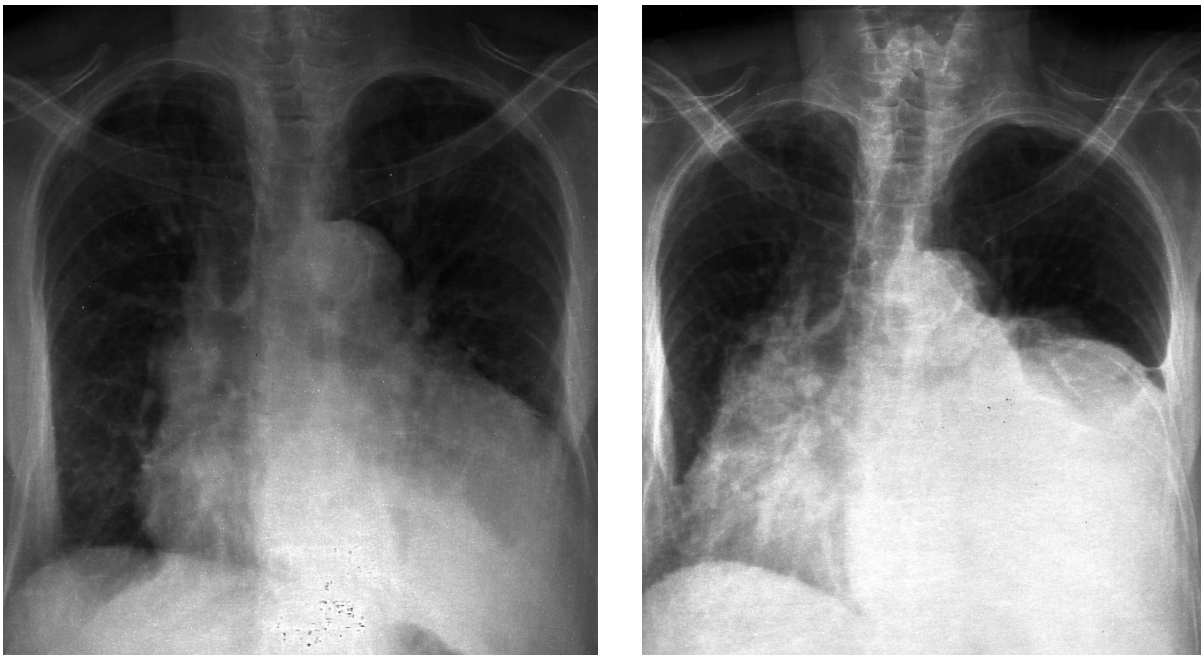


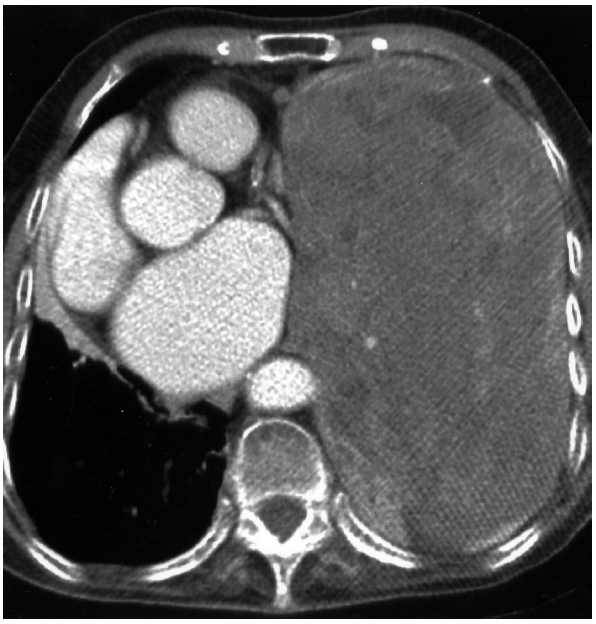
(A) (B)

Fig. 1. Chest radiographs showing (A) patient's condition 4 years prior to this admission, with left lower lung region patch and obscured left diaphragm, (B) condition before admission.

electron microscope. To date, there has been no clear evidence of a genetic predisposition, or of asbestos or tobacco exposure related to SFTP [5].

Case Report

A 79-year-old woman presented to our cardiology outpatient department with progressive dyspnea for 3 weeks. She was diagnosed as having congestive heart failure, NYHA stage B, and persistent atrial fibrillation 4 years prior to this outpatient department visit. She maintained regular follow-up at our cardiology outpatient department. Chest radiograph (Figure 1A) 4 years prior to this visit revealed left lower lung region patch with obscured left diaphragm. Left lower lung consolidation with pleural effusion was suspected at that time. In addition to the progressive dyspnea, especially on exertion, she also complained of general weakness, poor appetite and mild chest tightness. No fever, cough, body weight gain or leg edema was noted. With regard to the patient's recent contact history, her husband had pulmonary tuberculosis under complete treatment with isoniazid, ethambutol, and rifampin for 6 months and pyrazinamide for an initial 2 months 1 year prior to this outpatient department visit. She denied disease cluster history. On physical examination, her blood pressure was 119/51; pulse rate, 98 beats/min; respiratory rate, 26 breaths/min; and body temperature 36^{o}C. The conjunctiva was not pale. Traced jugular vein engorgement was noted. The breathing sounds showed crackles at the right lower lung region without wheezing. The abdominal wall was flat and soft without local tenderness. There was no finger clubbing



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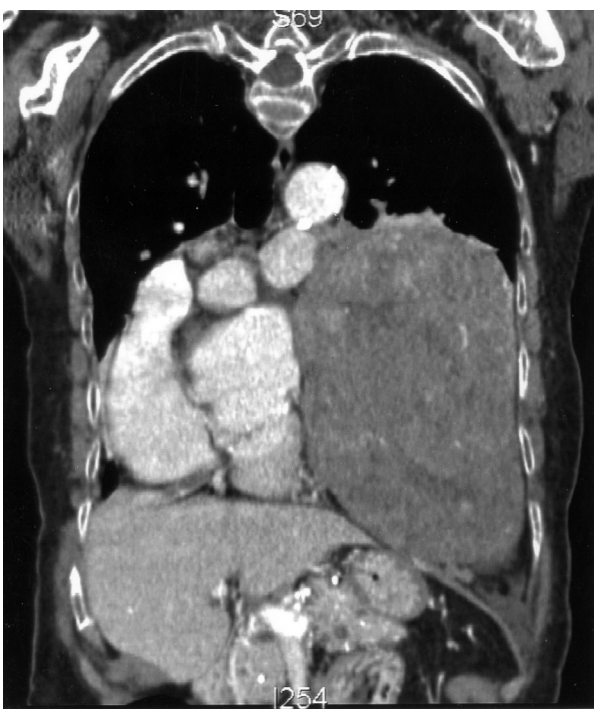


(B)

Fig. 2. Chest CT showing a huge left-sided broad-based solitary fibrous tumor of the pleura in the axial view (A), and coronal view (B).

or bone pain. The chest radiograph (Figure 1B) showed cardiomegaly, mediastinal widening, bilateral lower lung consolidation and a minimal amount pleural effusion on the left side. Therefore, she was admitted to our hospital for further management.

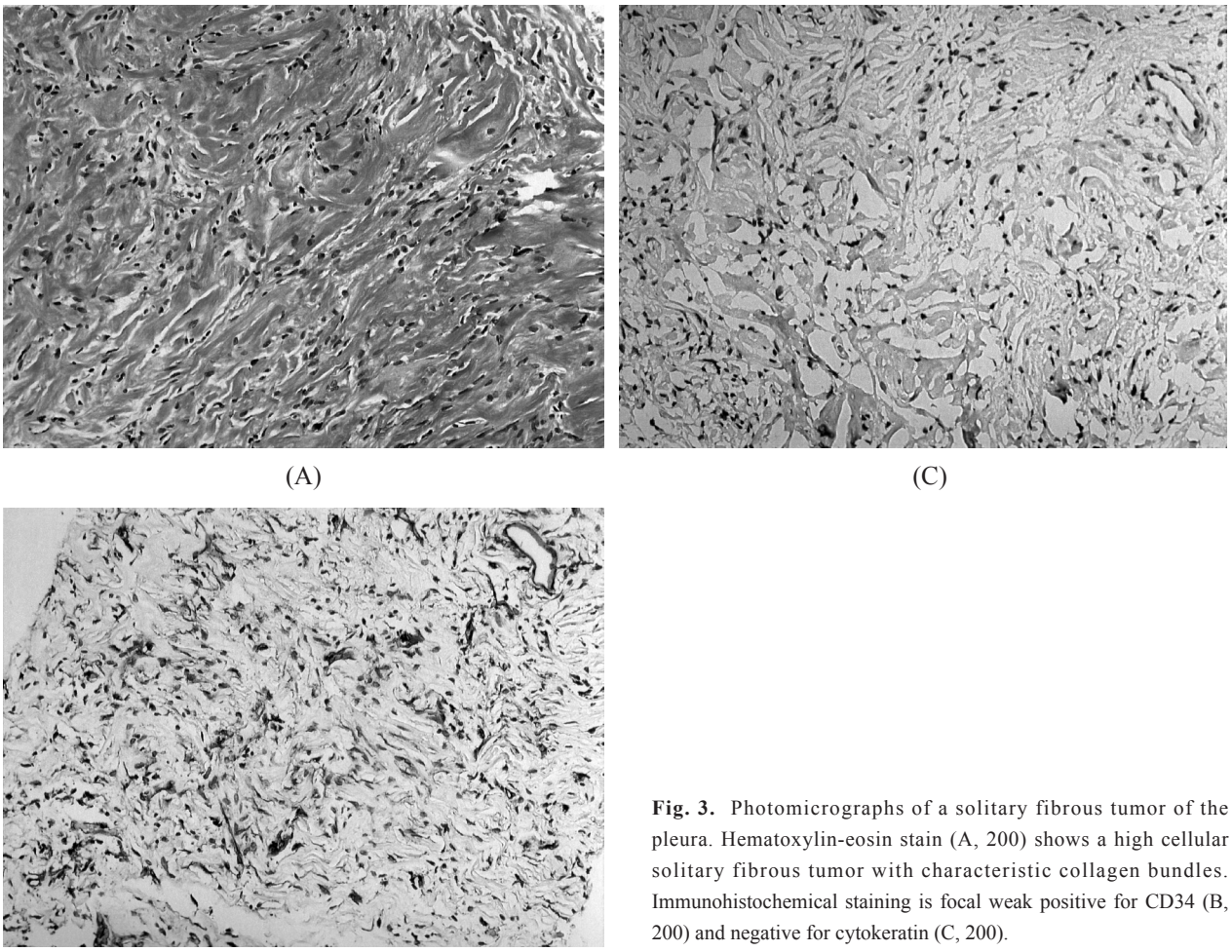
After admission, the following laboratory data were recorded: white blood cell count 8540 cell/μL (with neutrophil 76.5%); hemoglobulin level, 12.1 g/dL; platelet 281 K/μL; and pro-BNP (brain natriuretic peptide) 2840 pg/mL. The liver/renal function, serum glucose and electrolyte findings were all within the normal range. Empirical antibiotics were given for suspected community-acquired pneumonia. Acid-fast stain was negative for 3 sets. Cardiac echo showed LVEF 61.9%, PA max PG: 1.8 mmHg and normal right atrial and ventricle size. The left atrium and left ventricle were compressed by an extracardiac mass. The patient's dyspnea showed no obvious improvement. Due to persistent bilateral lower lung consolidation and mediastinal widening, chest computed tomography (CT) was performed, and a 15 cm hypervascular mass was revealed in the left lower lung zone with mediastinal shift to the right side and collapse of the left lower lobe. Chest ultrasound showed a huge subpleural heterogenous hypoechoic tumor in the left lower lung zone. Chest surgeon was consulted to discuss further operative management with her family. Surgical intervention was suggested, but she and her family refused operation due to advanced age. We performed echo-guided biopsy and the pathology report revealed a mesenchymal neoplasm with low cellularity, composed of collagen bundles. No epithelial component or lung tissue was noted. In the immunohistochemical exam, cytokeratin (AE1/AE3) was negative and the CD34 stain showed focal weak

positive. A mesenchymal tumor suggestive of solitary fibrous tumor was favored, based on the morphology and special stains. Under a relatively stable condition, she was discharged and received clinical follow-up at the hospice outpatient department.

Discussion

According to previous studies, more than 50% of patients with SFTP have no symptoms and the SFTP is identified as an incidental finding on radiographic examination [1]. However, a recent review [5] showed that the majority of patients (50-70%) present with some symptoms, commonly cough, chest pain, or dyspnea. Hemoptysis and obstructive pneumonitis, although rare, are also observed due to airway obstruction. Several paraneoplastic syndromes are reported to be associated with SFTP. Hypertrophic pulmonary osteoarthropathy (HPO) is the most common paraneoplastic syndrome in SFTP. HPO is reported in 14% to 19% of patients with SFTP, compared to a 5% incidence in lung carcinoma patients [1]. Patients with HPO commonly report bilateral arthritic-like symptoms, including stiffness or swelling of the joints, edema of the ankles, arthralgias, and pain along the long bones, especially in the tibias from the periosteal elevation. The symptoms generally resolve dramatically a few days after removal of the tumor. Up to 6% of patients with SFTP may present with hypoglycemic symptoms [5]. The hypoglycemia arises from the production by the tumor of insulin-like growth factor II (IGF-II) with insulin activity. A high serum level of IGF-II is typically associated with low levels of insulin; the serum insulin levels can also return to normal levels within a few days after resection of the tumor [3]. In our case, neither HPO nor hypoglycemia was noted.

The usual initial diagnostic test for SFTP is a chest radiograph. SFTP commonly has well-circumscribed margins. It is usually located near the lung periphery, and predominantly affects the middle/lower hemithorax (Figure 1). The chest CT scan is the key examination, because it more clearly shows the size and location of the tumor and aids in surgical planning (Figure 2). Magnetic resonance imaging (MRI) is helpful in differentiating the tumor from other structures and in confirming intrathoracic localization when the tumor abuts the diaphragm [6]. MRI findings are compatible with a fibrous tumor with a low signal on T1- and T2-weighted images. To date, there is still little information on the use of positron emission tomography (PET) to differentiate solitary fibrous tumors from malignant mesothelioma [7]. With the aid of an imaging examination, SFTP can be diagnosed or highly suspected if located at typical sites. The diagnosis of SFTP may be challenging sometimes when the lesion is located in an unusual site. The clinical value of biopsy before excision is still controversial. Some authors suggest that preoperative fine needle aspiration biopsy (FNAB) should not routinely be performed [1]. According to Cardillo *et al*. [5], the efficacy of FNAB is around 17-45%. In addition, a case in which a SFTP recurred with pleural seeding after an ultrasound-guided transthoracic biopsy was reported by Scarsbrook and colleagues [8]. However, it was the only case that mentioned tract seeding. In their histological appearance, the tumor cells of SFTP are elongated and spindle-shaped. About 10-20% of the cases reported in the literature were malignant [9]. With immunohistochemistry, the neoplastic cells are typically vimentin+, CD34+ and BCL2+, and are negative for cyto-



(A) (C)

(B)

Fig. 3. Photomicrographs of a solitary fibrous tumor of the pleura. Hematoxylin-eosin stain (A, 200) shows a high cellular solitary fibrous tumor with characteristic collagen bundles. Immunohistochemical staining is focal weak positive for CD34 (B, 200) and negative for cytokeratin (C, 200).

keratin (Figure 3).

Complete surgical resection is not only the preferred treatment for both benign and malignant SFTPs, but also the most important indicator of the clinical outcome of SFTP. VATS is useful in cases with small and pedunculated lesions. For large tumors (e.g. >10 cm diameter) or SFTP with a large broad base of attachment at the parietal pleura, thoracotomy is mandatory to achieve radicality in resection [4]. The tumor recurrence rate is about 2-21% (14-86% in malignant SFTP) and the 5-year overall survival rate ranges from 79 to 100% [5]. Currently, there is no systematic assessment of the role of adjuvant or neoadjuvant therapy in SFTP. De Perrot *et al*. [3] suggested a follow-up plan after resection of malignant SFTPs, with semi-annual radiologic follow-up by CT in the first 2 years and annually thereafter.

This patient presented with atrial fibrillation and dyspnea for 4 years before the diagnosis of a huge SFTP. According to Robinson [1], about 11-25% of patients with SFTP presented with dyspnea. The possible mechanism of dyspnea could be lung volume reduction due to the space-occupying tumor and infection as a result of airway obstruction. Therefore, the larger the tumor, the more likely that symptoms will

be present. To our knowledge, no patient with SFTP presenting as atrial fibrillation initially has been reported, and even a reported case with cardiac intracavitary metastasis [10] did not present with atrial fibrillation. We suppose that since the SFTP in this case was left-sided, it did not directly compress the right atrium.

In our case, the chest CT findings were suggestive of SFTP. Although FNAB efficacy is low, tissue proof was still necessary to determine further management for this patient, especially when she could not tolerate the surgical risk. Besides, there was no previous data to demonstrate the growth rate of the SFTP. In conclusion, SFTP are rare neoplasms that are benign 80-90% of the time. With complete surgical resection, SFTPs are curable, with a 5-year overall survival rate above 80%. Although about 30-40% of patients are asymptomatic when diagnosed, chest radiograph screening and chest CT for evaluation of tumor size and location are helpful in diagnosing SFTP. Biopsy should be done if disease management might be substantially affected by the results, or if surgical intervention is contraindicated and a diagnosis would alter treatment.

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巨大肋膜腔單發性纖維瘤－單一病例報告

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肋膜腔單發性纖維瘤是一種罕見的間質細胞腫瘤。它通常是無症狀的並常常在診斷前成長為一個巨大的腫瘤。有 10 至 20% 的肋膜腔單發性纖維瘤被診斷為惡性腫瘤。在完整的手術切除下，良性肋膜腔單發性纖維瘤是可以治癒的。臨床和影像學評估對於肋膜腔單發性纖維瘤的診斷可以有一定的幫助，但往往無法獲得明確的診斷。例行的細針穿刺活檢不建議用於肋膜腔單發性纖維瘤的診斷，這是由於診斷率低和可能的穿刺路徑上的轉移。然而，如果病理的結果將影響後續的治療或當手術是禁忌症時，病理組織切片仍是必要的。在此，我們報告一位 79 歲的婦女有漸進性呼吸困難的症狀，並在左下肺區發現巨大腫塊。病人及其家屬決定不接受手術治療。經由超音波指引的細針穿刺活檢，她被診斷出肋膜腔單發性纖維瘤。
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關鍵詞：單發性纖維瘤，肋膜腔腫瘤，預後

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