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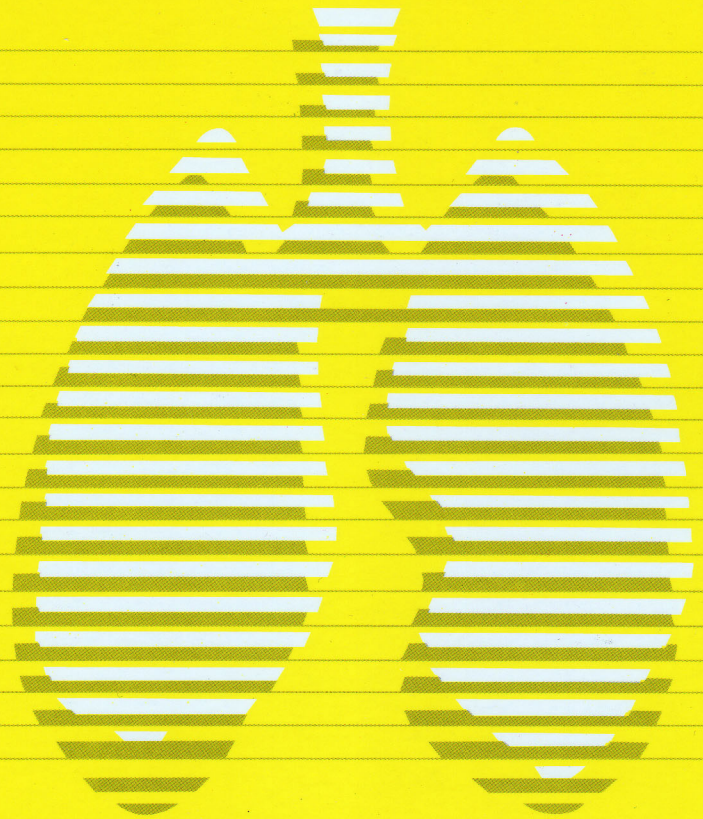

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Cigarette Smoking Increases the Risk of Latent Tuberculosis Infection: A Cross-Sectional Study in a TB-Endemic Area

Jia-Yih Feng*,**, Sheng-Wei Pan*,**, Shiang-Fen Huang**,***, Wei-Juin Su*,**

Introduction: An association between smoking and latent TB infection (LTBI) using the tuberculin skin test was noted in previous reports. The impact of smoking, including intensity and duration, on LTBI deserves further investigation with a more specific diagnostic tool: the interferon-γ release assay (IGRA).

Methods: From 2011 to 2013, individuals at high risk for LTBI and progression from LTBI to active TB were enrolled. LTBI was diagnosed by the QuantiFERON-TB Gold In-Tube test. Patients were categorized as never-smokers, ex-smokers or current smokers. The associations between smoking and LTBI were analyzed accordingly. The impact of smoke exposure on interferon-γ responses was explored as well.

Results: During the study period, we enrolled 1,037 patients in our analysis, including 167 ex-smokers, 152 current smokers, and 718 never-smokers. The proportions of LTBI among ex-smokers, current smokers, and never-smokers were 38.9%, 37.5%, and 23.4%, respectively; ever-smokers had a significantly higher incidence of LTBI than never-smokers (P<0.001). In multivariate analysis, both current smokers (OR 1.85, 95% CI 1.19-2.86) and ex-smokers (OR 1.66, 95% CI 1.06-2.60) were significantly associated with an increased risk of LTBI. After adjusting for related clinical factors, a dose-response relationship was found between LTBI and smoking duration (P_{trend}<0.001). The relationship between LTBI and smoking intensities was less consistent. Patients in the IGRA-positive population with higher smoking intensities had stronger interferon-γ responses. In the IGRA-negative population, the interferon-γ responses were comparable among patients with various smoke exposures.

Conclusions: Smoking significantly increases the risk of LTBI in high-risk individuals, especially those with a longer duration of smoking. ***(Thorac Med 2017; 32: 201-212)***

Key words: interferon-γ release assays, latent tuberculosis infection, smoking

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Introduction

Latent tuberculosis infection (LTBI) is a state of equilibrium in which host immunity can control the infection but is unable to completely eradicate the *Mycobacterium tuberculosis* (Mtb) [1]. Patients with LTBI possess immunological responses to Mtb proteins in the absence of clinical manifestations of active disease [2]. It is reported that 30% of individuals with Mtb exposure will have LTBI [3], and only a minority of them will have active tuberculosis (TB) disease progression. However, some individuals are regarded as a high-risk population because they have an increased likelihood of Mtb exposure or have clinical characteristics that increase their risk of active TB progression. These high-risk individuals should be considered for LTBI screening and treatment, if indicated [4-5]. The tuberculin skin test (TST) is the most commonly used traditional tool to diagnose LTBI. However, the accuracy of the TST can be interfered with by bacille Calmette-Guerin (BCG) vaccination and cross-reaction with non-TB mycobacterium (NTM) [6]. T-cell-based interferon-γ (IFN-γ) release assays (IGRAs) detect IFN-γ responses to Mtb-specific antigens and are currently preferred for use in persons with BCG vaccination [7].

Cigarette smoke is a well-documented risk factor for many respiratory disorders, including pulmonary TB [8-11]. Impaired local immune responses related to smoke exposure were found in a mice model and have been proposed as key factors contributing to the increased incidence of TB in smokers [12-14]. In Taiwan, the prevalence of smoking among active TB patients was around 30% to 40% [15-16]. Current or ex-smokers have also been identified to be at an increased the risk of LTBI [17-22]. Most studies have used the TST to diagnose LTBI, but the test has limited implications in TB-endemic areas with wide BCG vaccination exposure. However, smoking has been reported to be associated with false negative results in IGRAs [22-23]. This raises concerns regarding the use of the IGRA for LTBI detection in smokers, and as such, its use deserves further clarification.

For this study, we enrolled patients from a TB endemic area who were considered to be in high-risk groups for LTBI and TB disease development, and used IGRA for LTBI diagnoses. The main purpose of the present study was to evaluate the association between cigarette smoking, including intensity and duration, and the prevalence of LTBI in high-risk individuals. The impact of smoking and its intensity on IFN-γ response among these patients was analyzed as well.

Methods

Patients and settings

This cross-sectional observational study was conducted in a tertiary medical center in Taiwan from January 2011 to December 2013. Individuals who had an increased risk of acquiring LTBI or progressing to active TB were eligible for enrollment. These individuals included active TB contacts, health care workers, and patients with the comorbidities of malignancy, end-stage renal disease, liver cirrhosis, organ transplantation, and autoimmune diseases. Patients that presented with fibrocalcified lesions on chest radiographs that were indicative of prior TB disease were also included. A similar study population was analyzed previously to explore the association between gender and LTBI [24]. Patients with a history of anti-TB treatment, patients currently under anti-TB

treatment, patients who were recently diagnosed with active TB within 2 months after IGRA testing, pregnant women, those who were less than 20 years of age, and those with an uncertain smoking status were excluded. Data on demographic profiles and clinical characteristics were obtained from the patients through enrollment interviews. The patients' chest plain films were read by a chest physician who was blinded to patient data. The presence of fibrocalcified lesions that suggested past active TB disease was determined. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and written informed consent was obtained from each patient or their authorized representative(s) before enrollment.

Intensity and duration of smoking

Information regarding smoking past or present was obtained from the patients and/or their caregivers in the enrollment interview. Smoking-related data including average daily cigarette consumption, duration of the smoking habit, and history of quitting smoking were collected. An ever-smoker was defined as someone having smoked at least 1 cigarette a day for at least 1 year. An ex-smoker was defined as having stopped smoking for more than 1 year. A current smoker was defined as an ever-smoker who had smoked within the past year [8]. The dose-response relationships between LTBI and smoking intensity, smoking duration, and total smoke exposure (pack-years) were analyzed accordingly.

IFN-γ release assay

The diagnosis of LTBI was based on the IGRA, which was performed with the QuantiFERON-TB Gold In-Tube (QFT-GIT; Qiagen, Germany) test, according to the manufacturer's instructions. The details of blood sampling and performing the QDT-GIT test have been described in a previous study [24]. The test results were determined as negative, indeterminate, or positive (cut-off at 0.35 IU/ml), according to the manufacturer's software.

Statistical analysis

The data collected in the present study was analyzed using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA). Chi-square tests were used to calculate the differences in categorical variables between patients with varied smoking statuses. Independent *t* tests were used to calculate the differences in continuous variables. The independent variables were evaluated using a binary logistic regression model to identify the factors associated with the presence of LTBI. The odds ratios (ORs) with their 95% confidence intervals (CI) are presented. Variables with a *p* value less than 0.1 in the univariate analysis were selected to be entered into the multivariate model. In the dose-response analysis, daily cigarette consumption, smoking duration, and smoke exposure were categorized and modeled as indicator variables under multivariate logistic regression. The linear trend across categories of 1 smoking metric was assessed as a continuous variable, and the *p* value for trend was obtained from a Wald test of the coefficient of that continuous variable. All tests were 2-tailed, and a *p* value of less than 0.05 was considered to be statistically significant.

Results

Study population

During the study period, a total of 1,261 inpatients and outpatients from high-risk groups were eligible for recruitment. A study profile

showing the number of cases and reasons for exclusion is shown in Figure 1. In the end, 1,037 patients with determinate IGRA results, including 152 (14.7%) with recent active TB contact, 42 (4.1%) health care workers, 148 (14.3%) patients with diabetes mellitus, 354 (32.6%) with malignancy, 23 (2.2%) with end-stage renal disease, 47 (4.9%) with liver cirrhosis, 13 (1.3%) with a history of organ transplantation, 151 (14.6%) with autoimmune diseases and 214 (20.6%) patients with fibrocalcified lesions on chest radiographs, were analyzed in our study. Some of these patients had 2 or more risk factors. Among them, 167 (16.1%) were ex-smokers, 152 (14.7%) were current smokers, and 718 (69.2%) were never-smokers. The proportions

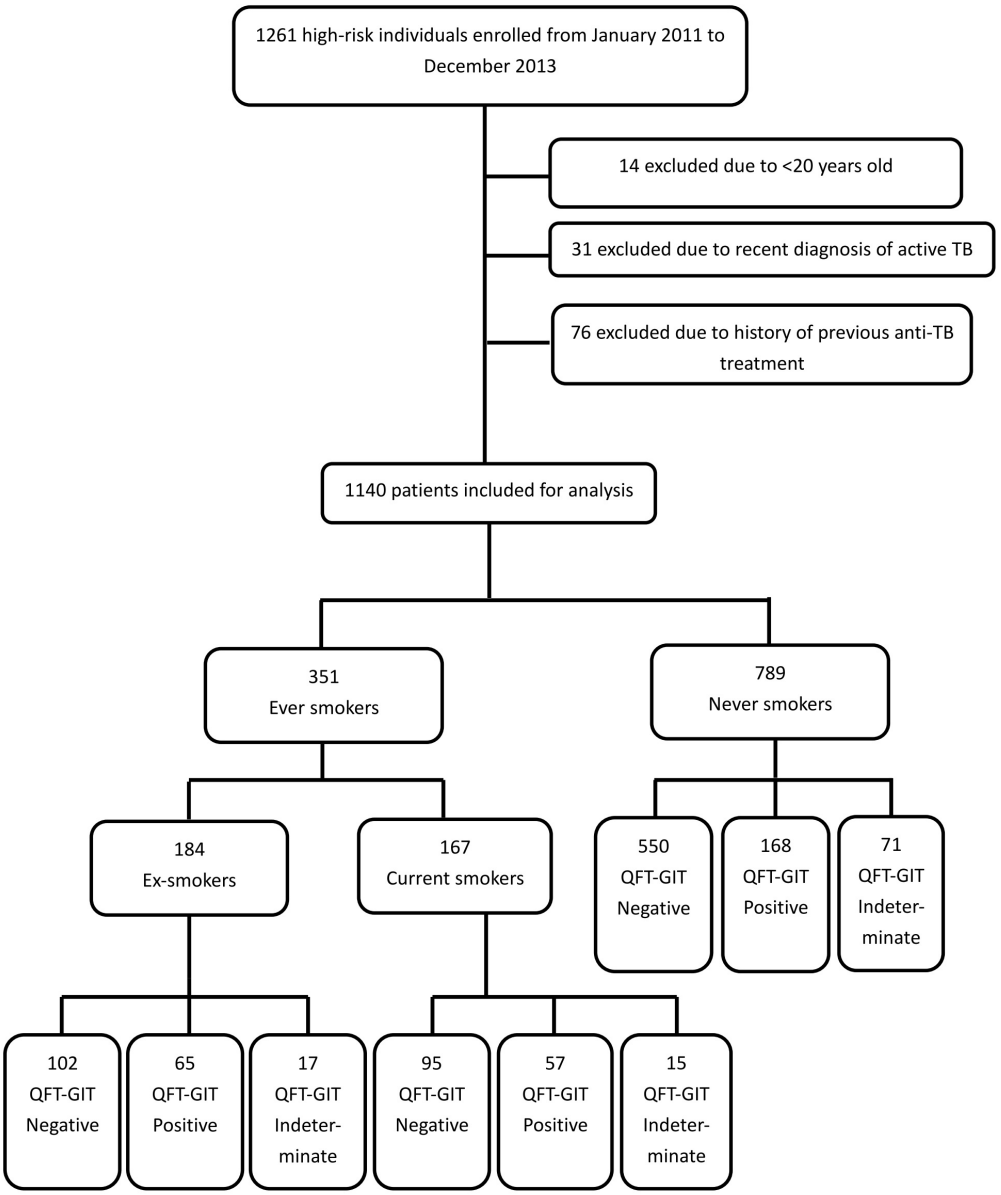

Fig. 1. Study profile presenting the number of cases and reasons for exclusion.

of LTBI cases were 38.9% (65/167) among ex-smokers, 37.5% (57/152) among current smokers, and 23.4% (168/718) among never-smokers.

Demographic characteristics and clinical factors associated with LTBI

Compared with never-smokers, patients with a smoking habit were older and were more likely to be male, have chronic obstructive pulmonary diseases (COPD), have some malignancies, and have fibrocalcified lesions. Patients with a smoking habit were less likely to have a recent TB contact history, have BCG vaccination, have some autoimmune disorders, and be health care workers. The proportion of LTBI was significantly higher in ex-smokers and current smokers (P<0.001) (Table 1).

In the univariate and multivariate analyses of the clinical factors associated with LTBI, we found that both ex-smoking (OR=1.66, 95% CI: 1.06-2.60) and current smoking (OR=1.85, 95% CI: 1.19-2.86) were independently associated with LTBI. Other clinical factors that significantly increased the risk of LTBI included older age (OR=1.01, 95% CI: 1.002-1.02) and presence of fibrocalcified lesions in the chest radiograph (OR=1.63, 95% CI: 1.17-2.28) (Table 2).

Intensity and duration of smoking

In multivariate analyses adjusted for age, gender, BCG vaccination, gastrectomy, and fibrocalcified lesions on radiographs, longer duration of smoking (OR 1.18, 95% CI 0.69-2.03 in ≤ 20 years smoking; OR 1.96, 95% CI 1.24-3.09 in > 20 and ≤ 40 years smoking; OR 2.58, 95% CI 1.48-4.48 in > 40 years smoking) was independently associated with the presence of LTBI, and the P_{trend} was <0.001. However, the impact of smoking intensity (cigarettes/day) and pack-years of cigarette consumption on LTBI was less significant and less consistent. We also found that patients with more severe pulmonary function impairment were independently associated with an increased risk of LTBI (OR 1.70, 95% CI 1.16-2.49 in ever-smokers without COPD; OR 3.00, 95% CI 1.30-6.90 in ever-smokers with COPD) (Table 3).

Impact of smoke exposure on IFN-γ responses

We then analyzed the IFN-γ responses to Mtb-specific peptides among never-smokers and ever-smokers with various smoke exposures, which were categorized by pack-years. The IFN-γ responses generally escalated with increasing smoke exposure (Figure 2). In the IGRA-positive population, patients with the highest degree of smoke exposure had the strongest response. In the IGRA-negative population, however, the IFN-γ responses were comparable between never-smokers and ever-smokers with various smoking intensities.

Discussion

In the present study, we investigated the impact of smoking on LTBI in patients at a high risk of developing LTBI and progressing to active TB disease. We found a significant association between smoking and LTBI diagnosed by QFT-GIT. In the multivariate analysis, smoking led to an increased risk of LTBI in both ex-smokers and current smokers, with ORs ranging from 1.66-1.85. When adjusted for age, gender, BCG vaccination and other clinical factors, we observed a dose-response relationship between LTBI and duration of smoking that was more significant and consistent than that due to the intensity of smoking. We also found that patients with higher smoking intensities had stron-

Table 1. Demographic Characteristics of the High-Risk Individuals Based on Smoking Status*

	Overall patients, n=1037	Smoking status			*P* value
		Never-smokers, n=718	Ex-smokers, n=167	Current smokers, n=152	
Mean age (SD)	58.9 (18.0)	55.6 (18.0)	71.2 (14.9)	61.2 (14.4)	<0.001
Male gender	542 (52.3%)	239 (33.3%)	162 (97%)	141 (92.8%)	<0.001
BMI (SD)	22.8 (4.2)	22.8 (4.2)	23.0 (3.8)	23.3 (4.5)	0.41
TB contact history	152 (14.7%)	130 (18.1%)	11 (6.6%)	11 (7.2%)	<0.001
BCG vaccination	688 (66.3%)	514 (71.6%)	75 (44.9%)	99 (65.1%)	<0.001
Health care worker	42 (4.1%)	42 (5.8%)	0	0	<0.001
Comorbid diseases					
Diabetes	148 (14.3%)	105 (14.6%)	25 (15%)	18 (11.8%)	0.65
COPD	33 (3.2%)	5 (0.7%)	16 (9.6%)	12 (7.9%)	<0.001
Malignancy	354 (34.1%)	160 (22.3%)	98 (58.7%)	96 (63.2%)	<0.001
Renal insufficiency	23 (2.2%)	15 (2.1%)	6 (3.6%)	2 (1.3%)	0.35
HIV-positive	0	0	0	0	-
Post-gastrectomy	19 (1.8%)	9 (1.3%)	5 (3.0%)	5 (3.3%)	0.11
Liver cirrhosis	47 (4.5%)	34 (4.7%)	6 (3.6%)	7 (4.6%)	0.81
Autoimmune disorder	151 (14.6%)	138 (19.2%)	8 (4.8%)	5 (3.3%)	<0.001
Organ transplantation	13 (1.3%)	11 (1.5%)	1 (0.6%)	1 (0.7%)	0.48
Fibrocalcified lesion in the upper lung field	214 (20.6%)	124 (17.3%)	56 (33.5%)	34 (22.4%)	<0.001
Latent TB infection	290 (28%)	168 (23.4%)	65 (38.9%)	57 (37.5%)	<0.001

*Data are presented as mean ± SD or n (%), unless otherwise stated.

BCG, bacille Calmette-Guerin; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; HIV, human immunodeficiency virus; TB, tuberculosis; SD, standard deviation.

ger IFN-γ responses to Mtb-specific antigens than those with lower smoking intensities.

Cigarette smoking is an important risk factor that leads to several systemic diseases, especially pulmonary disorders. Several large case-control studies and systemic reviews have reported an increased incidence of active TB in current and ex-smokers in recent years, with adjusted hazard ratios ranging from 1.5 to 2.9 [8-11]. In patients with active TB, smoking is associated with a worse treatment outcome, including delayed sputum conversion, more disease relapse, and higher mortality [25-28]. The negative impact of smoking on immunologic responses, such as impaired type 1 immunity, blunted antigen-presenting cells recruitment, enhanced Th2 immune responses, and increased bacterial burden, has been reported in animal and cell experiments [12-14]. Smoking may also impair the mucociliary clearance of pathogens in respiratory epithelium [29]. These adverse effects of cigarette smoking contribute to the higher incidence, more profound disease severity, and worse outcomes of active TB.

In contrast to TB, the roles of smoking on LTBI are less frequently analyzed. In a review

Table 2. Univariate and Multivariate Analysis of Clinical Characteristics Associated with Latent TB Infection in High-Risk Individuals Categorized by Their Smoking Status*

	Univariate analysis		Multivariate, ex-smoker	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Smoking status				
Never-smoker	1.00		1.00	
Ex-smoker	2.09 (1.46-2.98)	<0.001	1.66 (1.06-2.60)	0.027
Current smoker	1.96 (1.36-2.85)	<0.001	1.85 (1.19-2.86)	0.006
Male gender	1.40 (1.07-1.84)	0.016	0.92 (0.64-1.31)	0.64
Age	1.02 (1.01-1.03)	<0.001	1.01 (1.002-1.02)	0.022
BCG vaccination	0.65 (0.47-0.83)	0.001	1.03 (0.72-1.48)	0.86
Gastrectomy	2.93 (1.18-7.28)	0.021	2.31 (0.90-5.91)	0.08
COPD	2.21 (1.10-4.45)	0.026	1.32 (0.63-2.78)	0.47
Fibrocalcified lesion in chest radiogram	1.94 (1.41-2.66)	<0.001	1.63 (1.17-2.28)	0.004

*Odds ratios and 95% confidence intervals were derived from the logistic regression analysis.

OR, odds ratio; CI, confidence interval; TB, tuberculosis; BCG, bacille Calmette-Guerin, COPD, chronic obstructive pulmonary disorder.

study in which the diagnoses of LTBI were not based on IGRA, but on the TST, the pooled OR of smoking for LTBI ranged from 1.75 to 2.08 [30]. However, another study in South Africa reported that HIV-infected patients who were smokers were associated with decreased odds of being positive using an in-house IGRA [22]. In the present study, we included high-risk individuals from a TB-endemic area, and used IGRA to detect LTBI cases. We found that both ex-smoking and current smoking were independent predictors for LTBI in a multivariate analysis. Although current smokers were associated with a higher OR for LTBI than ex-smokers in our analysis, their risks of developing LTBI were comparable when we compared current and ex-smokers separately (data not shown). To our knowledge, this is the first large-scale study to analyze the impact of smoking on LTBI using IGRA with generally high-risk individuals. Our results are likely to be more reliable than those of previous reports that used the TST, particularly in areas with a prevalence of BCG vaccination.

We analyzed the roles of intensity and duration of smoking in LTBI. These factors have rarely been evaluated, and when they were evaluated, they had inconsistent results [18-19,21]. We observed a clear dose-response relationship between the duration of smoking and the risk of LTBI, using multivariate analysis that adjusted for age. In comparison, the impact of smoking intensity (cigarettes/day) and smoke exposure (pack-years) on the risk of LTBI was less consistent. A previous study of migrants in Vietnam and a population-based study performed in the United States also demonstrated that intensity of cigarette consumption was not significantly associated with increased risk of LTBI [18-19,21]. Our findings suggested that a longer duration of smoking, regardless of smoking intensity, may be more hazardous to local immunity against TB infection. The lung structure damage related to a longer duration may also be more profound

Table 3. Relative Risk of Latent TB Infection by Smoking Intensity, Smoking Duration, and Impairment of Pulmonary Function*, +

	All cases	LTBI cases, n (%)	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Cigarettes/day				
Never-smoker	718	168 (23.4%)	1.00	1.00
1-10	75	26 (34.7%)	1.79 (1.07-3.01)	1.52 (0.88-2.65)
11-20	156	67 (42.9%)	2.88 (1.97-4.19)	2.13 (1.37-3.32)
>20	88	29 (33.0%)	1.49 (0.86-2.57)	1.49 (0.86-2.57)
P_{trend}				<0.001
Years of smoking				
Never-smoker	718	168 (23.4%)	1.00	1.00
≤20	92	24 (26.1%)	1.16 (0.70-1.90)	1.18 (0.69-2.03)
>20 and ≤40	143	56 (39.2%)	2.11 (1.45-3.07)	1.96 (1.24-3.09)
>40	84	42 (50%)	3.27 (2.06-5.19)	2.58 (1.48-4.48)
P_{trend}				<0.001
Pack-years				
Never-smoker	718	168 (23.4%)	1.00	1.00
≤20	104	30 (28.8%)	1.33 (0.84-2.10)	1.23 (0.74-2.05)
>20 and ≤40	99	45 (45.5%)	2.73 (1.77-4.20)	2.40 (1.44-3.99)
>40	116	47 (40.5%)	2.23 (1.48-3.36)	1.88 (1.15-3.09)
P_{trend}				<0.001
Pulmonary function impairment				
Never-smoker	718	168 (23.4%)	1.00	1.00
Ever-smoker without COPD	291	107 (36.8%)	1.90 (1.42-2.56)	1.70 (1.16-2.49)
Ever-smoker with COPD	28	15 (53.6%)	3.78 (1.76-8.10)	3.00 (1.30-6.90)
P_{trend}				<0.001

*Odds ratios and 95% confidence intervals were derived from the logistic regression analysis.

+ Adjusted for age, gender, BCG vaccination, gastrectomy, and fibrocalcified lesions in the chest radiograph

OR, odds ratio; CI, confidence interval; LTBI, latent tuberculosis infection

than that from a higher intensity, which in turn increases the susceptibility to Mtb. Further *in vivo* or *in vitro* studies are warranted to elucidate the issue. Nevertheless, our results indicated that complete smoking cessation as early as possible is potentially an important measure to decrease the prevalence of LTBI, and should be incorporated into a TB control program.

Given the adverse impact of smoke exposure on local immunity against Mtb, concern regarding the diagnostic accuracy of IGRAs in LTBI patients with smoking habits has been raised. Oni *et al*. reported that HIV-infected patients who smoked were associated with a decreased odds of IGRA positivity [22]. Aabye *et al* reported that active TB patients who smoked had lower IFN-γ responses to TB antigen and a lower proportion of IGRA-positivity [23].

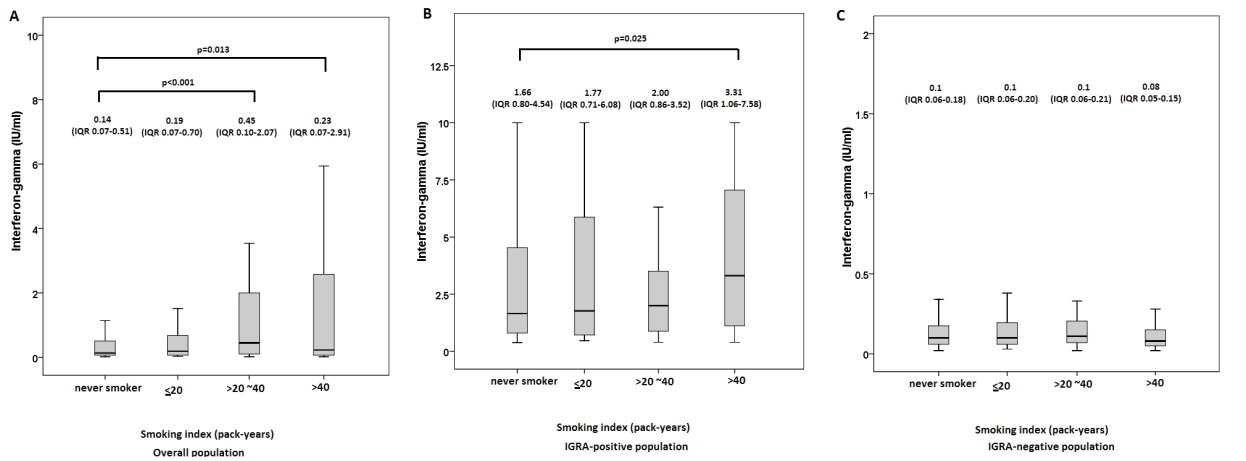

Fig. 2. Interferon-γ responses to Mtb-specific peptides in the (A) overall, (B) IGRA-positive, and (C) IGRA-negative population. Patients were stratified by smoke exposure (pack-years). Medians and interquartile ranges (IQR) are shown above each plot. Statistical significance was determined using the 2-sided Mann-Whitney U test. Mtb, *Mycobacterium tuberculosis*; IGRA, interferon-γ (IFN-γ) release assay.

The authors proposed that the suppressed T cell function associated with smoke exposure may lead to false-negative QFT-GIT results. Their speculation may partially explain our findings that smokers with the highest smoking intensities were not associated with the highest odds for LTBI. To elucidate the issue, we compared the IFN-γ responses of patients with various smoke exposures (pack-years). Our analysis revealed a positive correlation between IFN-γ response and the intensity of cigarette consumption in an IGRA-positive population. In IGRA-negative individuals, the IFN-γ responses were comparable between subgroups of patients. Our findings suggest that although smoke exposure may impair local immunity in the lung, the impact on IFN-γ responses of peripheral T cells was probably limited in non-HIV individuals. More studies comparing the reliability of IGRAs in HIV-infected and non-HIV infected smokers are needed to further clarify this issue.

There are several limitations to this study that are worth highlighting. We included patients with different risk factors rather than a specific high-risk population. Our participants were heterogeneous, but this also made our findings more applicable to populations generally at high risk for LTBI. As a TB-endemic area, remote unidentified active TB diseases in Taiwan are not uncommon and the IFN-γ response may be affected by the remote immune memory. We excluded patients with an anti-TB treatment history. Their impact was adjusted by including fibrocalcified lesions on chest radiographs in our multivariate model. We did not collect information on passive smoke exposure in our study, therefore the differences in impact between active and passive smoking could not be analyzed. Finally, IGRA cannot be used to differentiate recent or remote LTBI, so the differences in the impact of smoking on recent and remote LTBI could not be explored in the present study.

Conclusions

In summary, both ex-smoking and current smoking were independent risk factors for LTBI in high-risk individuals. The duration of smoking was positively correlated with an increased risk of developing LTBI, and this correlation was more significant and consistent than that of smoking intensity. Meanwhile, IGRA-positive patients with higher smoking intensity had stronger IFN-γ responses to Mtb-specific peptides. Our findings suggest that smoking is an important and modifiable risk factor for LTBI. The role of smoking cessation should be highlighted and integrated in TB-control programs in TB-endemic areas.

Acknowledgements

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抽菸增加潛伏結核感染風險－一個結核病盛行區的橫斷面研究

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前言：過去使用結核菌素測驗的研究顯示抽菸會增加潛伏結核感染的風險。但是使用丙型干擾素測驗分析抽菸與潛伏結核感染相關性的研究相對有限。

方法：自 2011 年至 2013 年收集潛伏結核感染高風險族群病人，以丙型干擾素測驗的結果診斷潛伏結核感染，分析病人抽菸情形與合併潛伏結核感染的相關性。

結果：在 1,037 位受試者中，有過去與現今抽菸史者的病人合併潛伏結核感染的比例顯著高於無抽菸者 (38.9% vs. 37.5% vs. 23.4%, *P*<0.001)。過去抽菸史 (OR 1.66, 95% CI 1.06-2.60) 與現今抽菸史 (OR 1.85, 95% CI 1.19-2.86) 都會顯著的增加潛伏結核感染的風險，而且會隨著抽菸時間的增加而上升 (P_{trend}<0.001)，但與每日抽菸量的相關性則較低。

結論：抽菸會顯著增加潛伏結核感染的風險，而且與抽菸的時間有正向的劑量反應關係。***(胸腔醫學 2017; 32: 201-212)***

關鍵詞：潛伏結核感染，抽菸，丙型干擾素測驗

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Good's Syndrome (Thymoma and Immunodeficiency): Report of 2 Unique Cases and a Literature Review

Chun-Hsiang Hsu*, Wen-Jen Lin*, Ruay-Sheng Lai*,**

Good's syndrome is defined as a thymoma with T-cell and B-cell immunodeficiency. Patients with Good's syndrome are susceptible to encapsulated bacterial, viral, fungal, and other opportunistic infections, and also frequently have autoimmune manifestations, such as myasthenia gravis, pure red cell aplasia, and other hematological abnormalities. Here, we report 2 cases of Good's syndrome with unique presentations: 1 patient presented with Kaposi sarcoma, the other with myelodysplastic syndrome (MDS). Both of our patients suffered from recurrent infections in spite of thymomectomy. One patient received monthly intravenous immunoglobulin replacement therapy, which decreased the number of infections. These cases can enhance our knowledge of a rare but potentially recurrent lethal infectious disease and our understanding of the unique presentations of Good's syndrome patients. ***(Thorac Med 2017; 32: 213-219)***

Key words: Good's syndrome, thymoma, immunodeficiency, intravenous immunoglobulin

Introduction

Good's syndrome is defined as a thymoma with immunodeficiency, and is present in less than 5% of patients with thymoma [6]. The defining features of Good's syndrome are increased susceptibility to various infections and manifestations of autoimmune diseases. The main immunological abnormalities include hypogammaglobulinemia, B-cell and CD4 T-cell lymphocytopenia, and a decreased CD4/CD8 T-cell ratio [7]. Early diagnosis and treatment of Good's syndrome are important for the prognosis. Immunological assays, including for lymphocyte subpopulations and quantitative immunoglobulins, should be performed in patients with thymoma and recurrent infections. Thymomectomy should be performed in most patients with thymoma to prevent locally invasive growth and metastasis; however, hypogammaglobulinemia in most patients does not resolve after thymomectomy. In order to reduce the risk of various infections, prophylactic intravenous immunoglobulin (IVIG) and antibiotics are recommended [7].

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Case Presentation

Case 1

A 50-year-old previously healthy man presented in September 2012 with a raised reddish nodular lesion on his right ankle for the past 2 months, and underwent an excisional biopsy. The pathological exam revealed a Kaposi sarcoma composed of a spindle cell proliferation with slit-like vascular spaces that was positive for HHV-8 immunostaining. Chest X-ray (Figure 1) and computed tomography (CT) revealed a solid mass at the left-side thoracic inlet (Figure 2). The mass was resected in September 2013, and pathologic examination revealed it to be an invasive thymoma, type AB. In September 2014, the patient was found to have panhypogammaglobulinemia with IgG levels of 316 mg/dL (normal: 751-1560 mg/dL), IgA levels of 13 mg/dL (normal: 82-453 mg/dL), and IgM levels of 33 mg/dL (normal: 46-304 mg/dL). Laboratory tests showed abnormal levels of CD4-positive cells (31%, normal: 35-55%) and CD19-positive cells (2%, normal: 5-15%), as well as an abnormal CD4/CD8 ratio (0.69, normal: 1.5-2) (Table 1). Bone marrow biopsy and immunostaining revealed normal morphology of the myeloid and erythroid series; thus, myelodysplastic syndrome (MDS) and pure red cell aplasia (PRCA) were excluded, and a diagnosis of Good's syndrome was made. The patient experienced recurrent surgical site infection, intractable tinea corporis, and *Haemophilus influenzae* pneumonia after thymomectomy. The patient has received IVIG replacement (400 mg/kg) monthly since September 2014, resulting in less frequent infections. There was no tumor recurrence in the follow-up period.

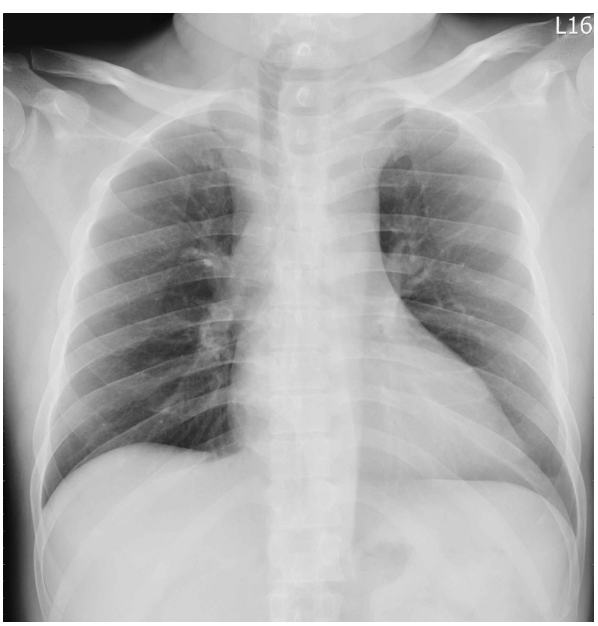

Fig. 1. Chest X-ray showed a widened mediastinum and right deviation of the trachea.

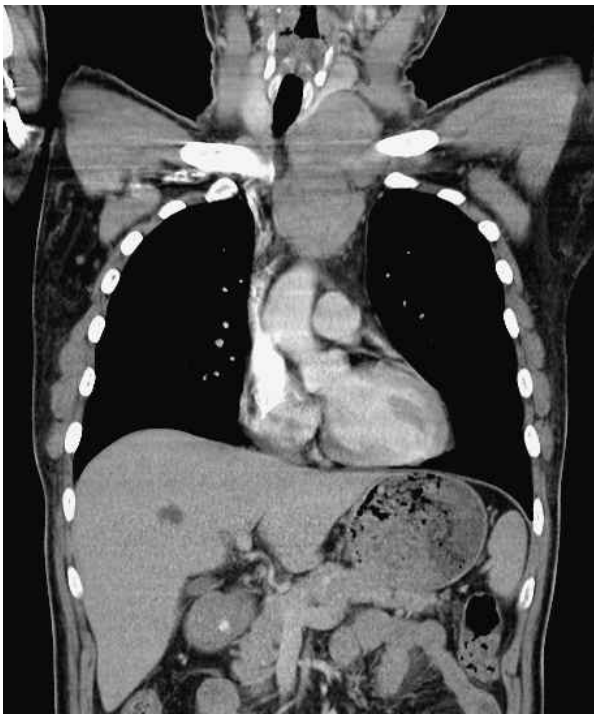

Fig. 2. Chest CT scan showed a solid mass at the left-side thoracic inlet.

Case 2

A 50-year-old woman initially presented

Table 1. Laboratory Results of the 2 Patients at Diagnosis

Parameters	Case 1	Case 2	Reference range
White blood cell ($\times 10^9$/L)	6.21	3.53	4-9.9
Hemoglobin (g/dL)	9.7	9.3	12.0-16.0
Mean corpuscular volume (fL)	57.3	94.0	80-95
Platelet ($\times 10^9$/L)	419	204	150-450
IgG (mg/dL)	316	752	751-1560
IgA (mg/dL)	13	166	82-453
IgM (mg/dL)	33	12	46-304
Lymphocyte subpopulations			
CD3+ (%)	82	92	65-85
CD4+ (%)	31	25	35-55
CD8+ (%)	45	61	20-36
CD19+ (%)	2	0	5-15
CD4: CD8 ratio	0.69	0.44	1.5-2
Blood smear interpretation	Unremarkable	Pelger-Huet-like cell (45%)	-
Human immunodeficiency virus	non-reactive	non-reactive	non-reactive
Antinuclear antibodies	negative	negative	negative

CD: cluster of differentiation; Ig: immunoglobulin

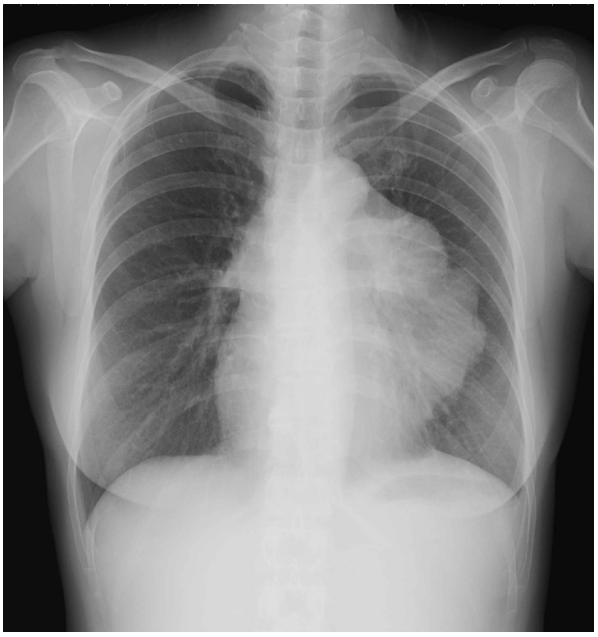

Fig. 3. Chest X-ray revealed a bulky hilum.

with a right auricular abscess in November 2006, which improved after surgical debridement and antibiotics. In September 2007, she was admitted for urinary tract infection with *E. coli* bacteremia. Chest X-ray (Figure 3) and CT (Figure 4) revealed a mediastinal mass. CT-guided biopsy showed type AB thymoma, so the patient underwent a thymomectomy in October 2007. Acute *E. coli* pyelonephritis, chronic diarrhea, multiple furuncles, and folliculitis on the trunk caused by *Staphylococcus aureus* developed frequently after thymomectomy. Laboratory tests showed an abnormal white blood cell (WBC) count (3.53×10^9/L, normal: $4\text{-}9.9\times 10^9$) and hemoglobin level, (9.3 g/dL, normal: 12.0-16.0), Pelger-Huet-like cells (45%, normal: 0), hypogammaglobulinemia with IgM (12 mg/dL, normal: 46-304 mg/dL), CD4-positive cells (25%, normal: 35-55%), CD19-posi-

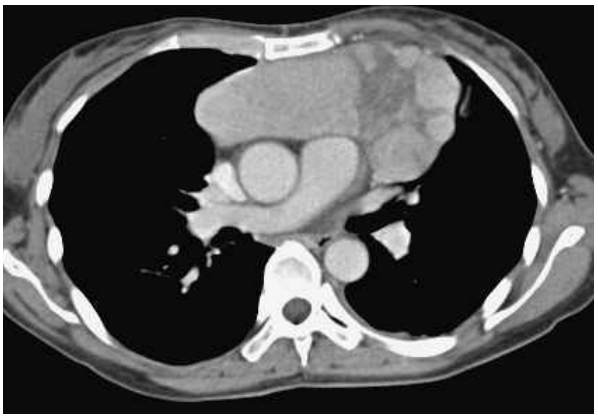

Fig. 4. Chest CT scans showed a mediastinal mass.

tive cells (0%, normal: 5-15%), and CD4/CD8 T cells, (0.44, normal: 1.5-2) (Table 1). The pathological diagnosis from the bone marrow examination revealed an increase in small-sized mononuclear megakaryocytes and numerous defective nucleus-bearing neutrophils without segmentation, compatible with a diagnosis of MDS. The patient experienced recurrent diarrhea, urinary tract infection, and *Pseudomonas aeruginosa* bacteremia, and received antibiotic therapy for infection control. The patient died of sepsis in January 2016.

Discussion

The pathogenesis of Good's syndrome remains incompletely understood. There are some proposed mechanisms, including dysregulated cytokine production and autoimmune destruction of hematopoietic precursors. One review study noted defects in T lymphocyte proliferation and IL-2 production in Good's syndrome patients in response to stimulation [8]. Another review study determined that T cells isolated from patients with thymoma inhibited immunoglobulin production by B cells in healthy controls [7]. Several studies have suggested that the pathogenesis of MDS is related to an autoantibody or CD8 T cells that directly target hematopoietic cells [9-10]. The survival of MDS patients with immunological abnormalities is significantly worse than the survival of those without immunological abnormalities [11]. Only 3 Good's syndrome cases with Kaposi sarcoma [2-4] and 1 with MDS have been reported [5]. In our 2 reported patients, we observed HHV-8 involvement in the development of Kaposi sarcoma (case 1), and the pathogenesis of MDS as an autoantibody or CD8 T cells that directly targeted hematopoietic cells (case 2).

Since there are defects in cellular- and humoral-mediated immunity among patients with Good's syndrome, pyogenic bacterial infection and opportunistic infections develop more frequently in these patients than in patients with other humoral immune defects (X-linked agammaglobulinemia or common variable immunodeficiency) [7]. Common bacterial pathogens causing recurrent sinopulmonary infections are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Pseudomonas* and *Klebsiella species*. Cytomegalovirus and herpes simplex virus are common opportunistic viral pathogens [1]. Compared to patients with common variable immunodeficiency, patients with Good's syndrome show a very late onset, have no family history, and display no lymphoid hyperplasia [12]. Most patients experience recurrent sinopulmonary infections, skin infections, bacterial diarrhea, and urinary tract infections [8].

Treatment of patients with Good's syndrome includes thymomectomy and IVIG replacement. Thymomectomy should be performed in most patients with thymomas to prevent local invasion and metastasis. Thymomectomy also has a favorable effect on myasthenia gravis and PRCA [1], but does not reverse the

Table 2. Reduction of Infections with Intravenous Immunoglobulin Therapy

	Number of cases	Reduction of infections
Kelesidis T, *et al*. 2010* [1]	152	38%
Tarr PE, *et al*. 2001 [8]	51	76.7%
Malphettes M, *et al*. 2015 [12]	21	53.8%
Kainulainen L, *et al*. 2010 [15]	12	41.7%
Sun X, *et al*. 2015 [16]	14	83.3%

* Review paper

immunological abnormalities associated with Good's syndrome [13]. Furthermore, thymomectomy may worsen hypogammaglobulinemia in some cases [14]. Some retrospective studies have suggested that IVIG reduces infection rates (Table 2). In order to reduce the risk of various infections, prophylactic IVIG is recommended [7].

In conclusion, Good's syndrome should be suspected in thymoma patients with autoimmune and hematological diseases who develop unusual infections. Early diagnosis of Good's syndrome is important for disease management. Immunological studies, including lymphocyte subpopulations and quantitative immunoglobulins, should be used for diagnostic evaluation of patients with thymoma and recurrent infections. Patients should be tested for toxoplasmosis and cytomegalovirus antibodies to evaluate the risk of reactivation [1]. For patients with Good's syndrome and recurrent infections, prophylactic IVIG infusion is strongly suggested to decrease the rate of infection.

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古德氏症候群（胸腺瘤合併免疫低下）－病例報告

許淳翔 * 林文仁 * 賴瑞生 *,**

古德氏症候群定義為胸腺瘤病患合併 T 細胞和 B 細胞免疫缺陷，患者易受夾膜性細菌，病毒，真菌和伺機性病原體的感染。部分患者也有自體免疫的表現，例如重症肌無力，純紅血球再生不良和其他血液學異常。我們報導二位古德氏症候群伴隨特殊表現的病患。對於胸腺瘤合併復發性感染的患者，應進行免疫學檢查，包括淋巴細胞亞群分析和定量免疫球蛋白。早期診斷及治療古德氏症候群對於預後有幫助。適合開刀的胸腺瘤患者應接受胸腺切除術，以防止局部浸潤和遠處轉移。大多數患者在胸腺切除術後，無法改善低丙種球蛋白血症。為了降低各種感染的風險，建議使用預防性靜脈內免疫球蛋白。希望藉由此病例報告能讓臨床醫師增加對此少見疾病的了解。*(胸腔醫學 **2017; 32: 213-219**)*

關鍵詞：古德氏症候群，胸腺瘤，免疫缺陷，靜脈注射免疫球蛋白

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Third-Generation Tyrosine Kinase Inhibitor Successfully Treated a T790M-Positive Lung Cancer Patient with Iris Metastasis – Case Report

Hian-Koon Chew*, Guan-Chin Tseng*****, Chun-Ju Lin**,******, Chen-Wen Su******, Chih-Yen Tu*,**,***, Te-Chun Hsia*,****, Wu-Huei Hsu*,**

Lung cancer with eye metastasis is very rare, especially metastasis to the iris. Approximately 21% of metastatic uveal tract tumors originate from the lung, and less than 10% of uveal metastases involve the iris. A 48-year-old Taiwanese female with the initial diagnosis of adenocarcinoma of the lung, stage IV, had redness and an itching sensation with tearing in the right eye for 1 week. The patient underwent ocular incisional biopsy of her right iris for suspected ocular metastasis. The pathology favored metastatic adenocarcinoma, which was consistent with the previous diagnosis of lung cancer. We successfully treated the metastatic iris tumor with a 3rd-generation tyrosine kinase inhibitor. The patient was still alive as of this writing, 1 year after metastasis to the iris was found. ***(Thorac Med 2017; 32: 220-225)***

Key words: lung cancer, iris, eye metastasis, T790M

Introduction

Lung cancer is the leading cause of cancer death worldwide. Common sites of lung cancer metastasis include the brain, pleural cavity, bone, liver, adrenal glands, contralateral lung, and skin. Metastatic tumors to the eye historically have been considered to be rare. Lung cancer has been reported to metastasize to the eye in 0.2% to 7% of lung cancer patients in clinical studies. In the eye, the uveal tract consists of the iris, which is located anteriorly, the ciliary body, and the choroid, which is located posteriorly; less than 10% of uveal metastases involve the iris [1-4]. The prognosis of these patients is rather poor. Median survival was 13 months after diagnosis of iris metastasis [5]. We present a case of metastasis to the iris in a patient with adenocarcinoma of the lung with acquired T790M-positive, which was treated

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initially with 1st-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy. We then made some changes to the patient's treatment regimen due to disease progression, and at last successfully treated the patient with osimertinib, a 3rd-generation TKI.

Case Report

This 48-year-old female non-smoker had an initial diagnosis of lung adenocarcinoma of the right upper lung (cT4N3M1a, stage IV) in August, 2013. The EGFR mutation result showed deletions in exon 19. Her chest x-ray revealed a mass lesion at the right upper lung (Figure 1A) with massive pleural effusion and multiple left lung metastases. The patient received EGFR-TKI therapy with gefitinib for 18 months. Pemetrexed and cisplatin were given 15 months later due to disease progression.

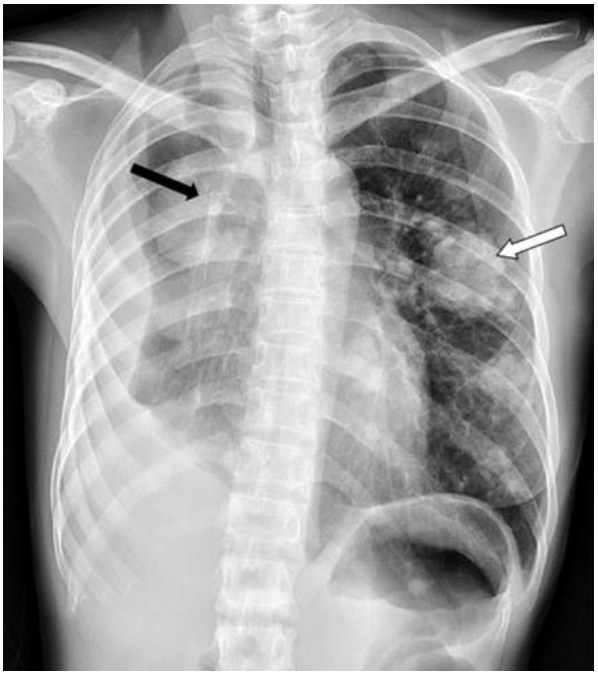

Fig. 1A. Chest radiograph revealed right upper lung cancer with left lung metastasis and right massive pleural effusion.

Then, we switched to erlotinib for 7 months, since the lung cancer had continued to progress. In August 2015, the patient underwent a chest computed tomography guided lung biopsy after erlotinib had failed to control her lung cancer. Pathology and molecular examination showed lung adenocarcinoma, and an EGFR deletion in exon 19 with T790M-positive, cytokeratin (CK)-7 (positive), thyroid transcription factor (TTF)-1 (positive), and anaplastic lymphoma kinase (ALK) (negative). Later, we prescribed afatinib, a 2nd-generation TKI, 40 mg QD, due to her worsening cough, other clinical deterioration, and the patient's wish.

After the treatment course described above, the patient presented at our ophthalmology outpatient department (OPD) in January 2016 with the primary complaint of redness and an itching sensation in her right eye, with tearing for 1 week. Her visual acuity was 20/20 in the right eye and 20/20 in the left eye. External ocular photography of the right eye showed a yellowish-colored tumor on the iris (Figure 2). Due to the finding of a right eye tumor, the patient underwent an incisional biopsy of the right eye. Pathology favored metastatic adenocarcinoma with a lung origin. The immunohistochemical study revealed the tumor cells were CK7 (positive), TTF-1 (positive), and CK20 (negative), and their appearance was similar to that of the lung. So, the iris lesion was diagnosed as a tumor that had metastasized from the lung cancer. The brain MRI also revealed brain metastasis, so the patient underwent whole-brain radiotherapy (WBRT), which yielded a good response 6 months later (Figure 3).

With the diagnosis of lung cancer in the anterior segment of the right upper lobe with eye and brain metastases, pT4N3M1b, stage IVb, the patient was given osimertinib (AZD9291)

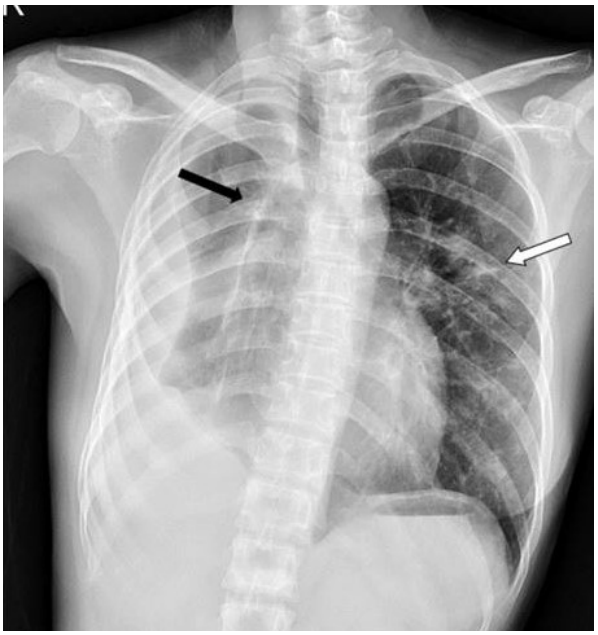

Fig. 1B. Remission after osimertinib medication. (black arrow: right upper lung cancer, white arrow: left lung metastasis)

of iris metastasis, the patient was still alive with regular follow-up at our chest and ophthalmology OPDs.

Discussion

Common sites of metastasis from lung cancer include the brain, bone, adrenal glands, contralateral lung, liver, pericardium, and kidneys. In a study on carcinoma metastatic to the eye and orbit, more than 1/2 of the tumors metastatic to the orbit were moderately well-differentiated adenocarcinomas [6]. Using a Mayo Clinic series (1948-1966), Henderson reported a total of 32 cases of metastatic carcinomas from among 465 orbital tumors (an incidence of almost 7%) [6]. In Ramon's study, the most

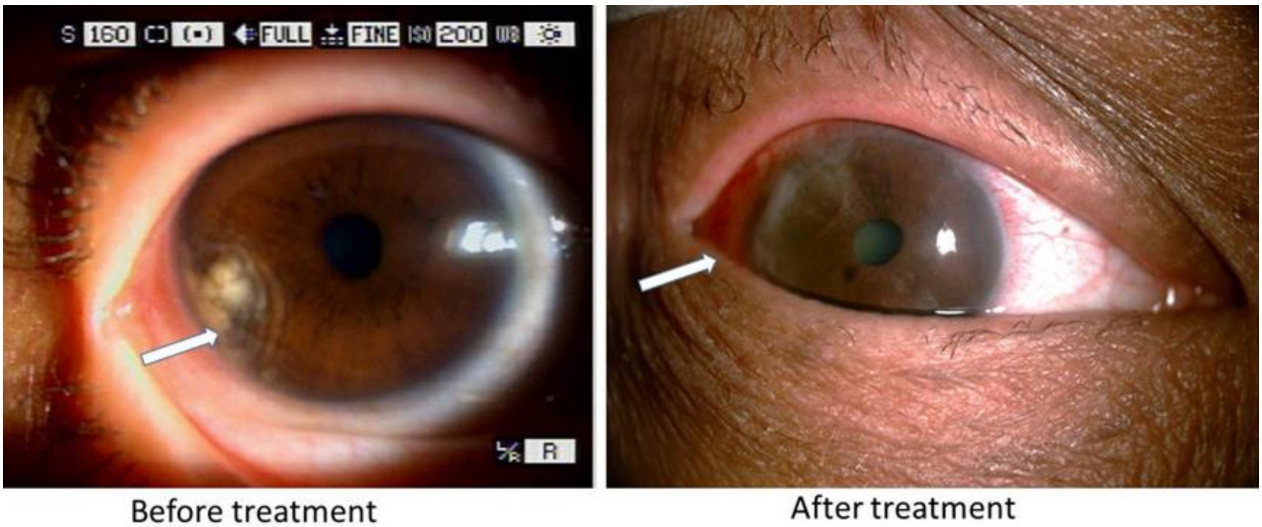

Fig. 2. External ocular photography showed a yellowish-colored tumor on the iris before ocular treatment, and shrinkage of the iris tumor after treatment.

80 mg po QD for co-mutation of T790M. The patient responded well to osimertinib (Figure 1B), with concomitant shrinkage of the right iris tumor (Figure 2). One year after the diagnosis

common site of primary tumor metastasis to the orbit was the lung in males, but the breast in females, and the lung was secondary to the breast as a site of metastasis to the orbit [6]. In another

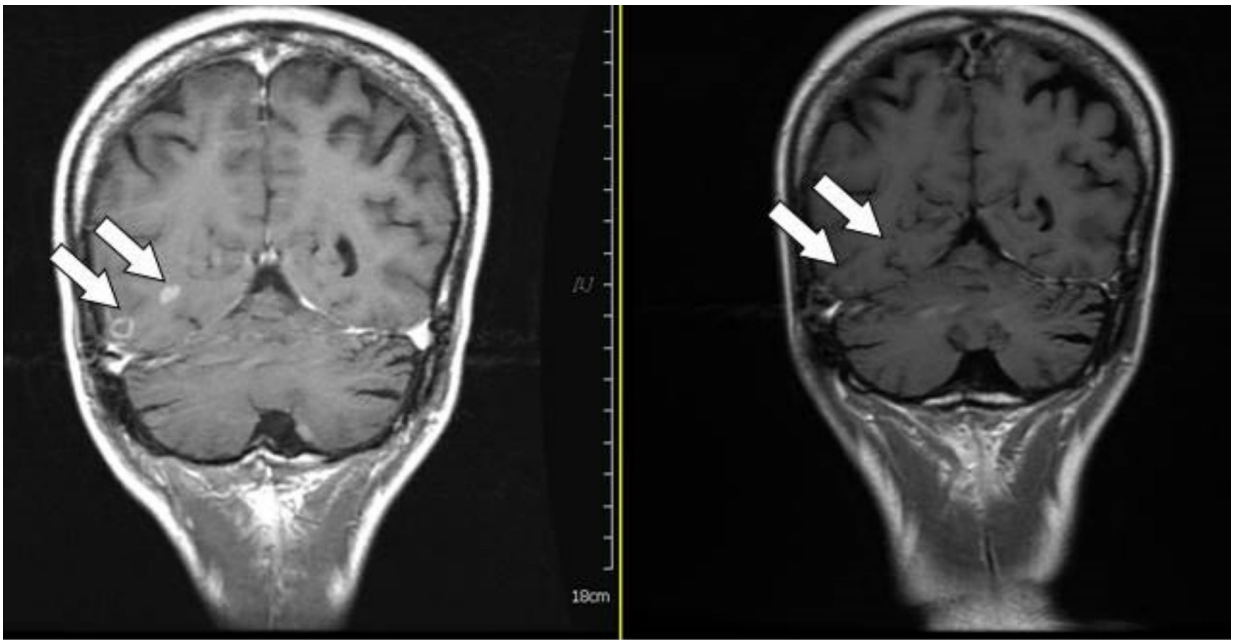

Fig. 3. Brain MRI showed brain metastasis status post-WBRT that responded well 6 months later, as shown by the arrow.

study, 91 of 1264 consecutive patients with orbital lesions had metastatic cancer to the orbit, accounting for 7% of the total [7]. Intraocular metastasis is commonly located in the posterior uvea, and rarely in the iris or in the ciliary body [8]. In our case, the intraocular metastasis was located in the iris. In another study, lung cancer was found to metastasize to the eye and orbit earlier than breast cancer (276 vs 1266 days, respectively), and the patients with lung cancer metastasis had a shorter median survival (188 vs 666 days, respectively) [9]. In a study by Meziani *et al*, 43 (39.4%) of 109 patients presenting with uveal metastasis were diagnosed with primary lung cancer. The uveal metastases were located within the choroid in 39 patients (90.7%), and in the iris in 3 patients (7.31%) [10]. The objective response rate to osimertinib in an independent review was 57% [11].

In conclusion, tumor of the iris metastatic from lung cancer is a rare tumor of the eye. The prognosis of patients with metastasis to the iris is poor because most of these patients have widespread disease. Despite extensive research and advances in lung cancer treatments, the prognosis is guarded, with a 5-year survival rate of 16%. The mean life expectancy after detection of uveal metastases was calculated to be 12 months.

In our case, the patient responded well to 3rd-generation TKI treatment with osimertinib (AZD9291), and has survived for 1 year, up to this writing, after the diagnosis of lung cancer with iris and brain metastases.

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第三代 TKI Osimertinib 成功治療一位 T790M 陽性之肺癌併虹膜轉移之病人－病例報告

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肺癌併眼部轉移非常少見，尤其是轉移到虹膜。大部分眼眶內轉移是發生在葡萄膜。有百分之二十一的葡萄膜腫瘤轉移是源自於肺部，小於百分之十的葡萄膜轉移牽涉及虹膜。在此我們描述一位四十八歲女性肺腺癌病人合併肺部，縱膈腔，肋膜，右眼及腦部的轉移。病人右眼發紅伴隨會癢及流淚約一個星期。她接受右眼虹膜切開術，腫瘤免疫螢光染色後發現 CK7 與 TTF-1 呈現陽性反應，確定為肺腺癌轉移至眼部。我們成功用第三代酪氨酸激酶抑制劑 Osimertinib 治療此轉移性虹膜腫瘤，病人從診斷出有虹膜轉移開始已健在地活了一年以上至今。*(胸腔醫學 **2017; 32: 220-225**)*

關鍵詞：肺癌，虹膜，眼部轉移，T790M

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Diffuse Large B-cell Lymphoma Presenting with Massive Pleural Effusion

Chi-Yi Lin*,**, Chun-Han Wu***, Chun-Hsiung Huang**, Tsai-Wang Huang*

Malignant lymphoma with pleural involvement affects 16% of patients with non-Hodgkin lymphoma during disease progression. Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma and accounts for approximately 24% of all cases. For lymphoma specified by site, primary effusion lymphoma is defined as lymphoid proliferations in the body cavities without extracavitary tumor masses, and accounts for 7% of all lymphomas. Primary effusion lymphoma is usually found in the pleural, peritoneal, and pericardial cavities, and even in the cerebrospinal fluid, and is universally associated with human herpes virus-8. We present the case of a 57-year-old man with diffuse large B-cell lymphoma with extranodal sites of involvement and pleural effusion who was negative for human immunodeficiency virus infection and not a recipient of an organ transplant. However, serology revealed he was positive for hepatitis C virus infection. The malignant pleural effusion was in complete remission after 3 cycles of R-CHOP chemotherapy. ***(Thorac Med 2017; 32: 226-231)***

Key words: diffuse large B-cell lymphoma, non-Hodgkin lymphoma, primary effusion lymphoma

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), and comprises around 24% of all cases of NHL [1-3]. DLBCL is more common in men and has an increasing incidence with age. The mean age at onset is approximately 60 years [3]. Patients can be asymptomatic or have a rapidly enlarging mass at the neck or abdomen, followed by the mediastinum. Patients may also present with fever, weight loss, night sweats, or other symptoms (B symptoms). DLBCL with at least 1 site of extranodal involvement accounts for 71% of all cases, and is associated with a poor overall survival rate [4]. The most common extranodal site of involvement is the soft tissue, followed by the bones, bone marrow, pleura, and stomach. The diagnosis of DLBCL is made by excisional biopsy from enlarged lymph nodes and is confirmed by histological findings. Malignant B cells express

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pan-B-cell markers, such as CD19, CD79a, CD20, PAX5, and CD22. Patients with DLBCL have chromosomal translocations in a variety of genes, including BCL6, BCL2, c-MYC, REL, and FAS [4].

Herein, we report the case of a patient who presented with extranodal DLBCL with pleural involvement but was negative for human herpes virus-8 (HHV8), human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV) infection. He had no chronic pyothorax and was not an organ transplant recipient.

Case Report

A 57-year-old Taiwanese man with a 20-year history of hypertension under medical control had developed progressively worsening right-sided chest pain on inspiration 2 weeks prior to this visit. He denied symptoms of fever, night sweating, and weight loss. He visited an emergency department in a regional hospital initially and underwent plain chest radiography. After observation of massive pleural effusion, he underwent insertion of a 14-Fr pigtail catheter and was transferred to our institute. His blood tests showed a normal white blood cell (WBC) count ($7.32\times10^3/\mu L$) and albumin level (4.0 g/dL) but elevated levels of C-reactive protein (CRP) (6.58 mg/dL) and lactate dehydrogenase (LDH) (288 U/L). Plain chest radiography revealed several pleural-based opacities in the right lung field and at the site of insertion of the pigtail catheter (Figure 1).

We collected his pleural effusion for further investigations, including biochemistry, cytology, and bacterial culture. Lymphocytes were the only predominant cells, and no infectious organism was found. Abdominal ultrasonography revealed splenomegaly and fatty infiltration in the liver parenchyma. Chest-to-abdomen computed tomography (CT) showed irregular and nodular thickening of the bilateral pleura with right-sided pleural effusion (Figure 2). In addition, multiple hypodense lesions (minimum: 1.6 cm, maximum: 5 cm) were visible in the omentum, spleen, and pancreatic tail.

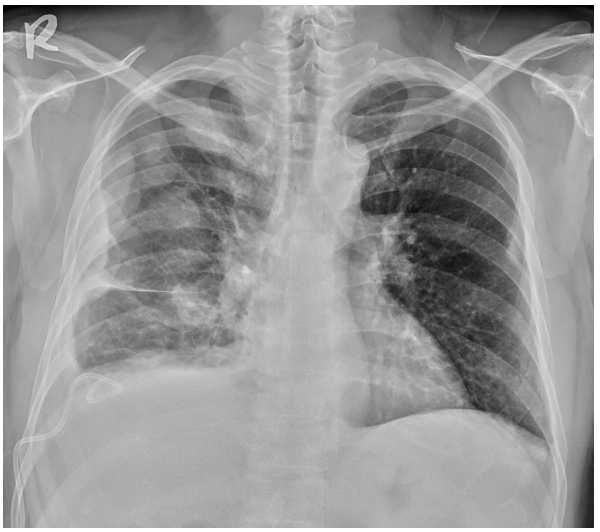
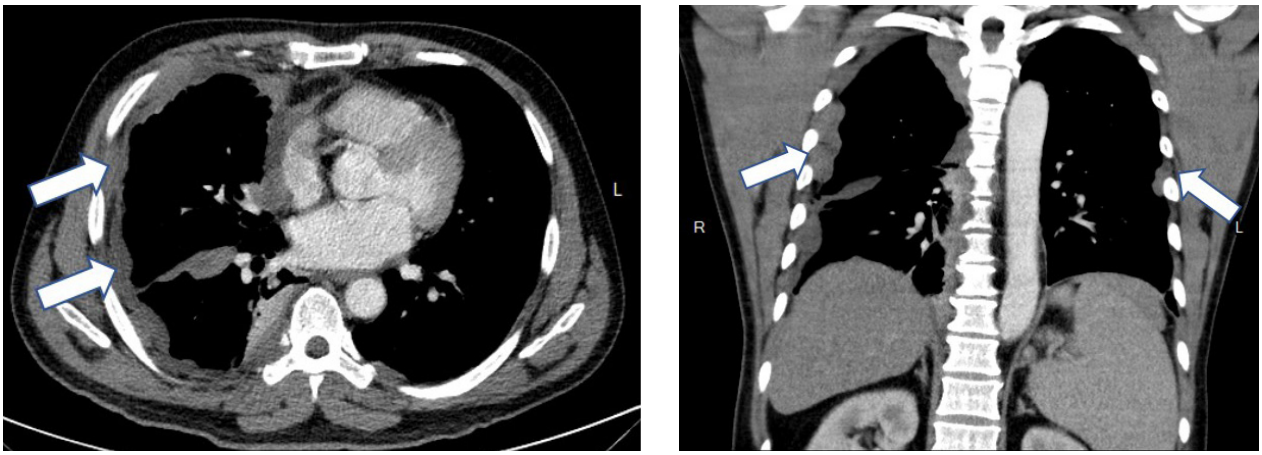


Fig. 1. Chest radiograph shows several pleural-based opacities in the right lung field and at the site of insertion of the pigtail catheter.

The pleura biopsy showed high-grade malignant B-cell lymphoma, positive for CD20 and BCL2 (Figure 3). The serologic studies were positive for anti-hepatitis C virus (HCV) antibody but negative for tuberculosis, cryptococcus, aspergillus and HIV infection.

Brain magnetic resonance imaging (MRI) and a technetium 99m-methyl diphosphonate (Tc99m MDP) bone scan revealed no evidence of brain or bony metastases. The 18-fluoro-2-deoxyglucose positron emission tomography (18F-FDG-PET) showed multiple hypermetabolic foci in the thoracic and abdominal cavity, especially in the right thorax (Figure 4). Bone marrow aspiration revealed tumor cell infiltration.



(A) (B)

Fig. 2A-B. Computed tomography scan shows bilateral loculated pleural effusion (arrows) with right lower lobe atelectasis (A. axial view; B. coronal view).

The first adjuvant chemotherapy regimen comprising rituximab (375 mg/m^2), endoxan (750 mg/m^2), doxorubicin (50 mg/m^2), vincristine (2 mg/m^2), and prednisolone (100 mg/day), i.e., R-CHOP, was administered during hospitalization. After treatment, the patient had scanty pleural effusion and was discharged; thereafter, he followed up at our oncological out-patient department every month. His malignant pleural effusion was in complete remission after 3 cycles of chemotherapy and his DLBCL showed a complete response on a whole body PET scan after 6 cycles of chemotherapy.

Discussion

Malignant lymphoma with pleural involvement accounts for 16% of all NHL cases [1-2]. Primary effusion lymphoma (PEL) is defined as lymphoma involving the pleural, peritoneal, and pericardial space, and even the cerebrospinal fluid without lymphadenopathy or tumor masses. PEL is strongly associated with HHV8 [5,8,11], and sometimes, it occurs in EBV- and HIV-infected individuals [1-2,6,8]. PEL accounts for 7% of all lymphomas [13] and has been reported in elderly patients negative for HIV [6,8,11]. The pathogenesis is still uncertain but may be related to chronic inflammation causing stimulation of malignant B-cells [2]. Mucosa-associated lymphoid tissue (MALT) lymphoma occurs prior to DLBCL in most cases with PEL [1,3,9]. High grade B-cell lymphoma, such as DLBCL, accounts for up to 19% of cases of PEL [1,3]. Other rare causes of PEL include follicular lymphoma, Burkitt's lymphoma, and T-cell lymphoma. However, the findings in our case do not fit the criteria of PEL. In the past 10 years, cases of HHV-8-negative primary lymphomatous effusions have been described and were called HHV-8-unrelated PEL-like lymphomas, which are associated with HCV infection [13]. In our case, virology revealed the patient was positive for HCV infection only. Due to the possibility of lymphomatous effusion secondary to systemic lymphomas, the diagnosis of HHV-8-unrelated PEL-like lymphomas was excluded temporarily. However, the relationship between

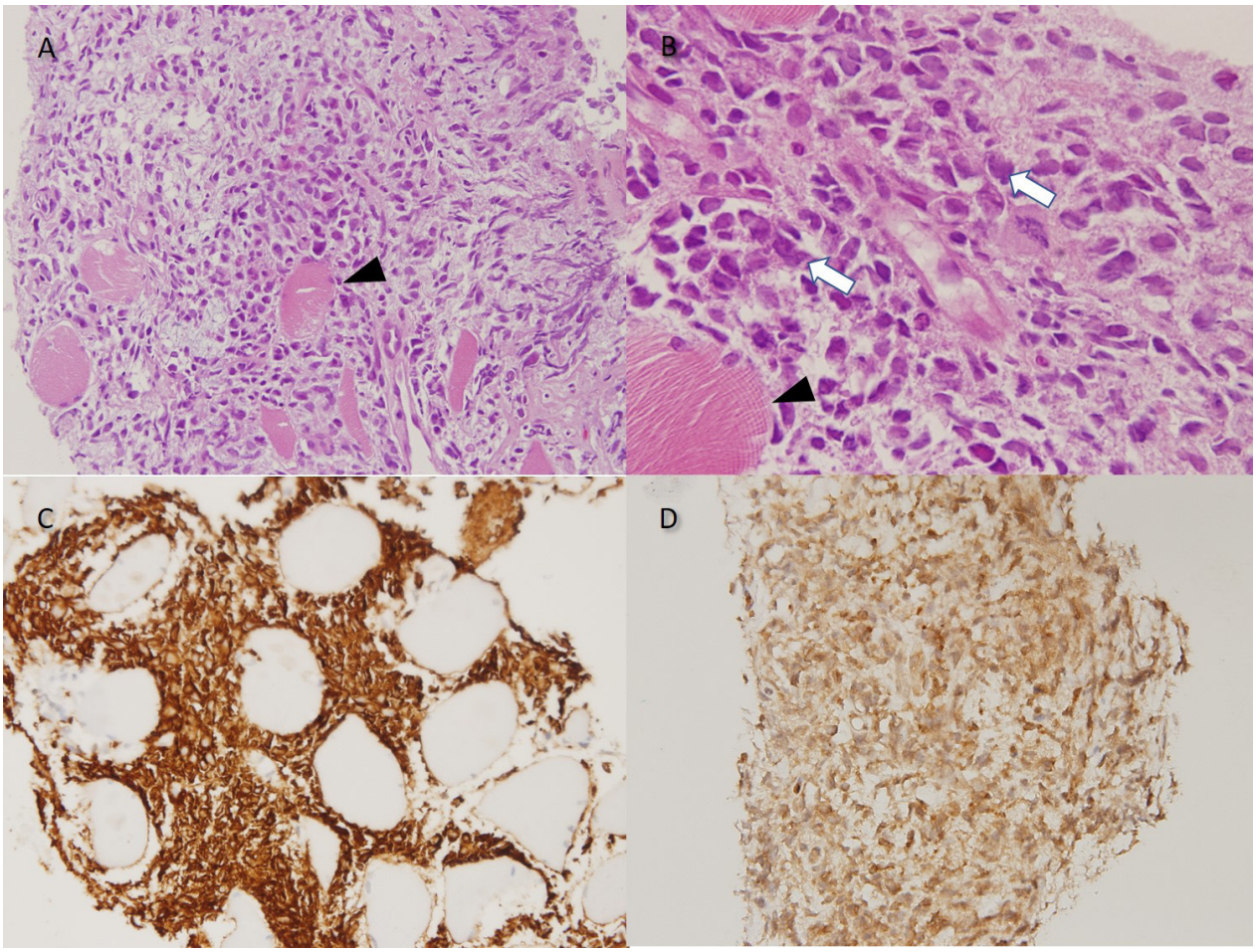


Fig. 3A-D. Pathological findings of pleural biopsy in cellblocks. A, B. Many large cells with irregular nuclei (arrows) and loosening skeletal muscle (arrow head; H&E staining, original magnification ×400 and ×1000). C. Many tumor cells show strong positive expression of CD20 (original magnification ×400). D. Focal tumor cells show positive expression of BCL2 (original magnification ×400).

HCV infection and DLBCL cases needs further study.

In the National Comprehensive Cancer Network (NCCN) guidelines for NHL, the presence of pleural effusions or peritoneal ascites is a criterion of a poor prognosis. YP Chen *et al*. reported that around 18% of DLBCL cases with serous effusions have a poor prognosis [10]. In the Japanese literature, the median survival time of NHL patients with pleural involvement was approximately 8 months; survival was shorter in patients who did not undergo treatment than in patients undergoing drainage and receiving rituximab-containing chemotherapy [11]. In our case, we performed a secure diagnostic procedure involving pleural biopsy via a minimal approach and a bone marrow biopsy.

It is important to establish a more effective and less toxic treatment for DLBCL. In a retrospective study, the R-CHOP regimen without consolidative radiotherapy achieved a high cure rate in approximately one-half of primary mediastinal large B-cell lymphoma (PMBL) cases. For PMBL cases with a high International Prognostic Index score and/or the presence of pleural or pericardial effusion, the 4-year overall

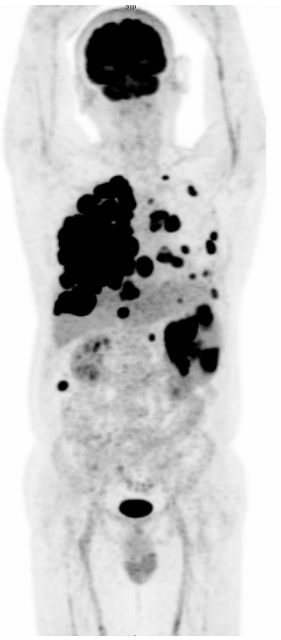


Fig. 4. Whole body PET scan shows multiple hypermetabolic foci in the thoracic and abdominal cavity (especially in the right thorax).

survival rate and progression-free survival were 81% and 54%, respectively [12]. In our case, the patient completed 6 cycles of R-CHOP chemotherapy and his pleural effusion was in complete remission after the third cycle of chemotherapy.

Conclusions

Although DLBCL cases with pleural involvement are rare, aggressive diagnostic investigations and effective treatment are beneficial to the patient's prognosis. Precise diagnosis via thoracoscopy and aggressive chemotherapy with a R-CHOP regimen resulted in a good outcome.

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瀰漫性大型 B 細胞淋巴癌合併大量胸水病例報告

林祈邑 *,** 吳俊漢 *** 黃俊雄 ** 黃才旺 *

惡性淋巴癌病肋膜侵犯約占非何杰金氏淋巴癌病患的百分之 16。瀰漫性大型 B 細胞淋巴癌是非何杰金氏淋巴癌中最常見的次分類，約占百分之 24。根據淋巴癌原發的部位，原發積液淋巴瘤定義為惡性淋巴增生在體腔部位而沒有體腔外的腫塊，發生率約占總淋巴癌的百分之 7。常見侵犯部位在肋膜腔、腹膜腔、心包膜腔及甚至在腦脊髓液中，並且與人類疱疹病毒第 8 型感染有密切相關。我們報告一例 57 歲男性診斷為瀰漫性大型 B 細胞淋巴癌合併淋巴結外侵犯及肋膜積水，本身無人類免疫缺乏病毒感染且非器官移植的接受者。然而，血清學上指出病人有 C 型肝炎病毒感染。在第三次輔助性化學治療（R-CHOP）結束後他的肋膜積液的症狀得到完全緩解。*(胸腔醫學 **2017; 32: 226-231**)*

關鍵詞：瀰漫性大型 B 細胞淋巴癌，非何杰金氏淋巴癌，原發積液淋巴瘤

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Angiosarcoma of the Pericardium Presenting with Recurrent Pneumothorax: A Case Report and Review of the Literature

Ying-Shou Chen, Chien-Wei Hsu, Huai-Pao Lee*, Szu-Pei Ho*, Rui-Sheng Lai

Angiosarcoma is the most common primary malignant type of primary cardiac neoplasm. It is an extremely rare condition that arises from the pericardium even more rarely than from the heart. We present the case of a 44-year-old man with progressive bilateral infiltration of the lungs, recurrent pneumothorax, and multiple brain nodules. Transthoracic echocardiography revealed a suspicious mediastinal mass lesion that compressed the right ventricle and caused pericardial effusion. Pericardiocentesis yielded a bloody fluid for which pathologic findings were negative. The patient underwent palliative surgery for cardiac tamponade and advanced biopsy. Pathology confirmed a pericardial angiosarcoma. The prognosis of this disease is usually poor. Surgical resection is the primary treatment for localized cancer. As yet, no randomized, controlled trials have established the roles of chemotherapy, radiotherapy, and immunotherapy for this rare disease. ***(Thorac Med 2017; 32: 232-237)***

Key words: cardiac tumor, pericardial angiosarcoma, pneumothorax

Introduction

The most common malignant cardiac tumors are metastases. Primary heart tumors are rare, and of these, primary angiosarcomas are extremely rare, with an incidence of 1.7/100,000 cases [1]. Angiosarcomas very rarely arise from the pericardium. The symptoms of this disease are non-specific, and include shortness of breath, fever, malaise, and chest pain. Diagnosis of an angiosarcoma of the pericardium is very difficult – it is often delayed, and is generally based on the clinician's suspicion. The main diagnostic tools currently available are echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI). Only a few small datasets describing treatment modalities have been published, and standard regimens have not been defined. The prognosis of this disease is very poor [2-3]. We present a case of

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pericardial angiosarcoma with recurrent pneumothorax that highlights the difficult diagnosis and treatment.

Case Report

A 44-year-old male patient with no previous medical history was referred to our hospital with recurrent right-side pneumothorax, progressive lung infiltration, and a post-mechanical ventilation status of acute respiratory failure.

The patient had maintained normal health until approximately 2 months before admission, when he developed a dry cough with occasional hemoptysis. A non-contrast-enhanced chest CT exam performed approximately 6 weeks before admission revealed multiple lung nodules without other specific findings (Figure 1). The patient had been treated with oral voriconazole (450 mg/day) for suspected pulmonary cryptococcosis, based on a high serum Cryptococcus antigen titer (serum Cryptococcus Ag=1:2048). However, approximately 2 weeks before admission, he presented at another hospital with spontaneous right-side pneumothorax, which remitted without further surgical intervention after the insertion of a thoracostomy tube. This condition recurred 3 days before admission. During a second hospitalization at another hospital, multiple brain nodules were identified, in addition to progressive bilateral lung infiltration (Figure 2). The patient underwent emergency intubation with mechanical ventilation for acute -onset hypoxic respiratory failure. He was subsequently admitted to our respiratory intensive care unit for management.

Besides the second serum sample, the cerebrospinal fluid Cryptococcus antigen titer was negative. Progressive hypoxemia persisted during his hospitalization. A chest X-ray indicated bilateral pneumothorax with extensive infiltration (Figure 3). Hypoxemia did not improve significantly even with thoracostomy tube drainage, as well as antibiotic and antifungal treatment. His pneumothorax also occurred off and on, even with adequate placement of the chest tube. We began venovenous extracorporeal membrane oxygenation (ECMO) for progressive hypoxemia, despite ventilator settings

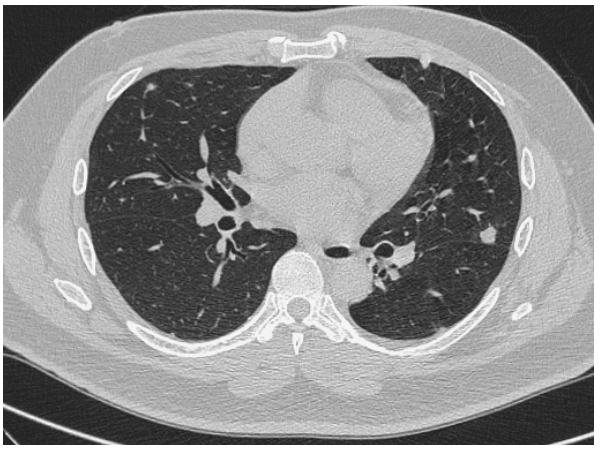

Fig. 1. Non-contrast enhanced chest CT obtained 2 months before admission. Multiple lung nodules are indicated.

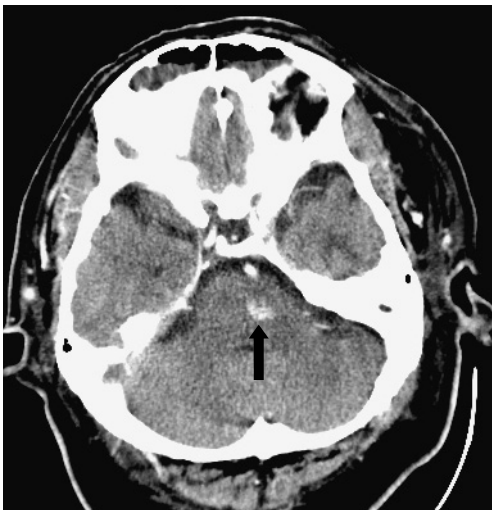

Fig. 2. Enhanced nodule (black arrow) with focal edema in the left pons of the brain.

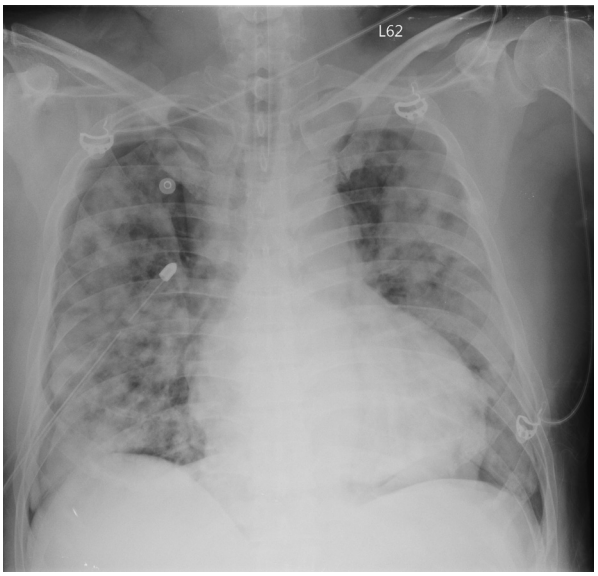

Fig. 3. Antero-posterior chest X-ray obtained at admission, showing post-thoracostomy right-side pneumothorax with extensive bilateral infiltration.

optimization. Transthoracic echocardiography (TTE) revealed the presence of a suspicious mass at the mediastinum that caused significant cardiac compression, especially of the right ventricle. Follow-up thoracic CT indicated a new onset pericardial mass with hemorrhage that caused cardiac tamponade (Figure 4).

A laboratory evaluation and transbronchial brushing revealed some atypical cells. Left-side exudative (LDH: 698 U/L, protein: 2.3 g/dL, sugar: 138 mg/dL) non-hemothorax effusion (ratio of pleural effusion to blood hematocrit: 27%) with negative cytology was reported. The patient was considered qualified for bone marrow aspiration and pericardiotomy with incisional biopsy to collect samples and achieve cardiac decompression. Immunohistochemical staining of the bone marrow and pericardium indicated positivity for the endothelial markers CD31 and CD34 (Figure 5). A diagnosis of angiosarcoma was finally confirmed. Unfortunately, the patient died several hours after surgery due to massive, uncontrolled bleeding.

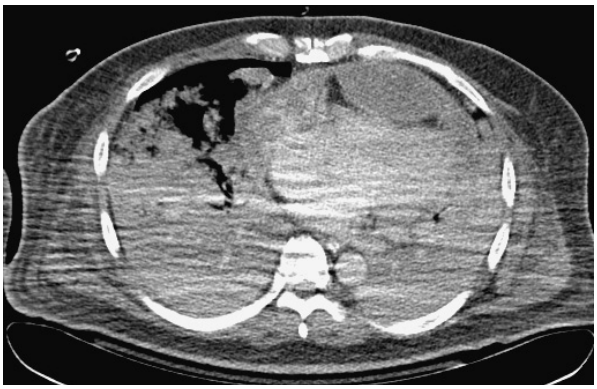

Fig. 4. Pericardial mass (star) with hemorrhage that caused right heart compression.

Discussion

Primary cardiac malignancy is rare, and few relevant studies are available. According to previous autopsy data, the incidence of this condition is only 0.001-0.030% [4]. Metastasis or direct invasion of the heart is more common. The most common primary heart tumors are atrial myxomas, which comprise 75% of affected cases [5]; the remaining 25% are malignant, and of those, 3/4 are sarcomas. The most common malignant primary cardiac tumors are angiosarcoma, rhabdomyosarcoma, malignant mesothelioma, and fibrosarcoma [2,5].

Angiosarcoma is the most frequently occurring type of sarcoma in adults, and is male-predominant. Metastases of these tumors are common and widespread, consequent to exposure to systemic circulation [2,4]. Most angiosarcomas have already metastasized to the lung, liver, and brain at the time of presentation [6]. Although the symptoms and signs are non-specific, a primary cardiac tumor should be considered in the differential diagnosis of valvular disease, congestive heart failure, and arrhythmia [2,4].

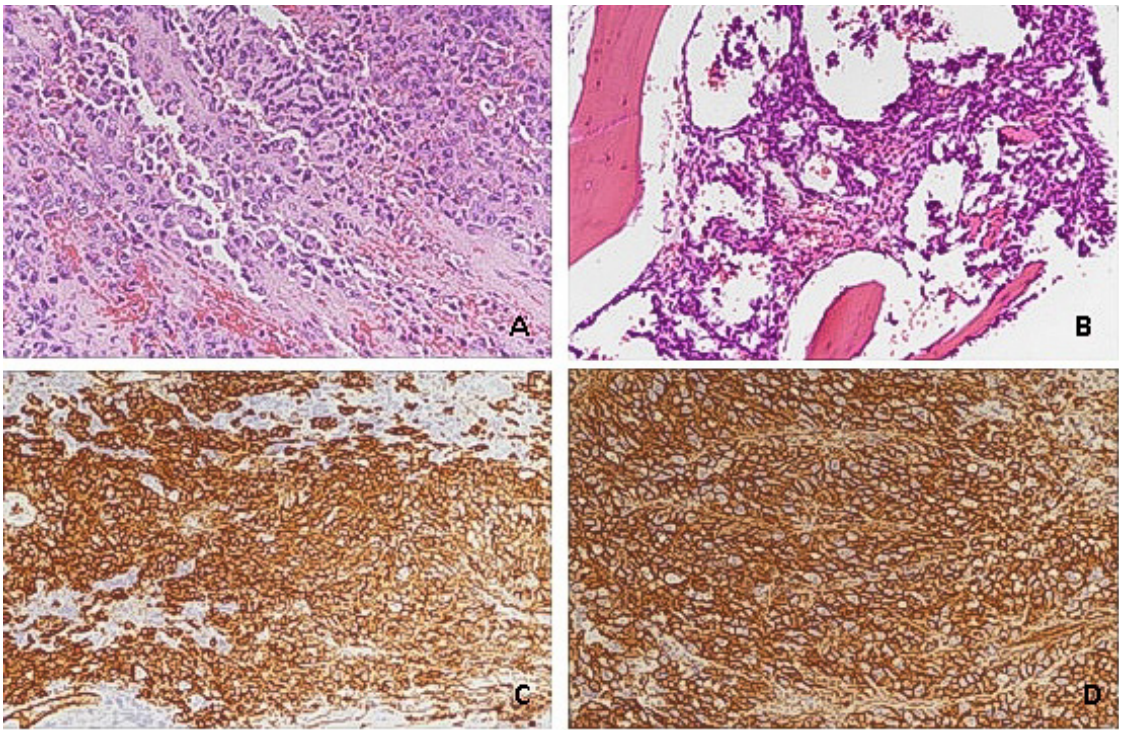

Fig. 5. Immunohistochemistry staining. A: Pericardial angiosarcoma containing anastomosing vascular channels lined with epithelioid neoplastic cells exhibiting marked cytologic atypia and increased mitotic activity. B: Hypercellular bone marrow. The trilinear hematopoietic cells have been replaced with atypical vascular spaces lined with endothelial cells containing abundant cytoplasm, large vesicular nucleoli, and prominent nucleoli. Positive immunostaining of the tumor cells for (C) CD31 and (D) CD34.

The classic triad includes- symptoms and signs of intracardiac obstruction, signs of systemic embolization, and systemic or constitutional symptoms- such as fever, arthralgia, and myalgia [5,7-9].

The diagnosis of cardiac tumors requires a high level of suspicion, given the rarity of this condition [2,4]. The main diagnostic tools currently include TTE and transesophageal echocardiogram, MRI and CT. Echocardiography can identify the involvement and competency of valves, the function of ventricles, irregular thickening of the pericardium, and intracavity masses that interfere with blood flow [10-11].

MRI and CT scans can provide additional information about metastases and tumor resectability [3,9]. CT yields a relatively high degree of tissue resolution, which facilitates characterization. Cardiac MRI can visualize the tumor extent, as well as vascular and pericardial involvement [9].

In terms of morphology, angiosarcomas are usually hemorrhagic with poorly defined borders. These lesions often invade contiguous structures, including the vena cava and tricuspid valve [3]. The affected vascular structures are lined with pleomorphic and atypical cells. Higher mitotic rates and necrosis indicate a poorer outcome [12]. Immunohistochemical staining reveals, these tumors are positive for factor VIII, Von Willebrand factor, and CD31 [13].

Angiosarcomas causing severe obstruction or intractable arrhythmias should be resected immediately, if possible [2,4]. However, no standard treatment has been established because of the rarity of these tumors and the lack of large randomized, controlled studies. Although surgical resection is a mainstay of treatment, local tumor invasion often increases the difficulty of complete resection and leads to discouraging results [14]. The efficacies of chemotherapy and radiation alone have not been widely reported [15]. According to a limited study, preoperative chemotherapy might play a role in tumor reduction, thus rendering the lesion more resectable and eliminating micro-metastases [14]. However, the efficacy of adjuvant chemotherapy is not well -established. In a study of 6 patients, adjuvant chemotherapy was not associated with better outcomes, compared to surgery alone. Very few patients have been treated with heart transplantation, so the results are not definite, and no survival benefit has been observed [16].

Generally, heart transplantation is not recommended because of the small number of donor organs and the extensive list of potential recipients without malignancy, the morbidity and mortality involved with immunosuppression, and the potential effect of immunosuppression on any remaining malignancy [2,4].

Angiosarcomas of the heart exhibit aggressive behavior, and generally have a very poor prognosis. Approximately 90% of patients die within 9-12 months after diagnosis without resection. Our patient presented a rapidly growing angiosarcoma of the pericardium and had an unclear initial diagnosis. Few studies have reported recurrent pneumothorax as a presentation of this disease. An early aggressive diagnostic modality is needed to provide an opportunity for treatment and to improve survival in patients with this type of aggressive cancer.

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臨床表現爲反覆性氣胸之心包膜血管肉瘤：病例報告與文獻回顧

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原發性心臟惡性腫瘤相當罕見。其中以血管肉瘤為最常見的組織型態。而心包膜的血管肉瘤更為罕見。我們報告一名 44 歲男性病患，以反覆性氣胸、進展性肺浸潤與腦部結節來表現。經胸腔心臟超音波顯示疑似縱膈腔腫瘤合併右心壓迫與心包膜積液。心包膜穿刺抽取積液呈現出血但是細胞病理為陰性。為治療心包膜填塞與取得檢體，病患接受緩解性手術。病理結果證實為血管肉瘤。血管肉瘤的預後非常差。若腫瘤為侷限性，仍以手術為主要治療方法。也由於該疾病相當罕見，故仍無大型研究去證實其他治療，如化學治療、放射治療與免疫治療等療效。*(胸腔醫學 **2017; 32: 232-237**)*

關鍵詞：心臟腫瘤，心包膜血管肉瘤，氣胸

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Reversed Halo Sign in Cryptogenic Organizing Pneumonia: A Case Report and Literature Review

Chiu-Fan Chen*, Huai-Pao Lee**,***, Kuo-An Chu*, Ruay-Sheng Lai*,****

The reversed halo sign is a computed tomography image pattern characterized by a central ground-glass opacity surrounded by a complete or near-complete ring of consolidation. It is a rare and special sign of organizing pneumonia. Although an increasing number of other pulmonary diseases have been reported to have this image pattern, organizing pneumonia still accounts for the largest number of cases. Here, we report a typical case of reversed halo sign in biopsy-proven cryptogenic organizing pneumonia, and briefly review the current literature regarding this rare image pattern. Other important differential diagnoses for a reversed halo sign are tuberculosis and invasive pulmonary fungal infections. Immune status and several associated radiological features could effectively differentiate possible causes. The reversed halo sign in tuberculosis is always associated with nodular lesions on or within the rim. The reversed halo sign in invasive pulmonary fungal infection occurs mostly in immunocompromised patients, and is strongly associated with ring thickness > 1 cm, reticulation within the lesion, and pleural effusion. Based on these factors, we suggest the reversed halo sign is very useful as a guide for the diagnosis of organizing pneumonia, tuberculosis, and invasive pulmonary fungal infections. ***(Thorac Med 2017; 32: 238-244)***

Key words: computed tomography, cryptogenic organizing pneumonia, reversed halo sign

Introduction

Organizing pneumonia (OP) is a non-infectious inflammation affecting the alveolar space, interstitium, alveolar wall, and distal bronchiole. The pathology of OP reveals inflammatory cells infiltration with abnormal proliferation of fibroblasts and myofibroblasts, and granulation tissue formation with intra-alveolar fibroblastic plugs. Sometimes the granulation tissue may extend into the distal bronchioles, resulting in lumen occlusion [1]. OP can be cryptogenic or occur secondarily to various lung injuries, such as those due to connective tissue disease, infection, drug-use, or malignancy [2]. The most common computed tomography (CT) patterns

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are bilateral multiple patchy consolidations or ground-glass opacities, which are usually subpleural and may be migratory. Less common image patterns are focal, mass-like consolidations, or a diffuse infiltrative pattern with mixed alveolar and interstitial opacities. The reversed halo sign (RHS) is a rare but special pattern of OP. On chest CT, the RHS appears as a central ground-glass opacity surrounded by a circular consolidation [1-2]. In this report, we present an illustrative case of RHS in biopsy-proven cryptogenic organizing pneumonia (COP), and include a brief summary of recently published literature.

Case Report

The patient was a 36-year-old woman who had an abnormal chest X-ray during her health exam. She denied fever, smoking, respiratory complaints, extra-pulmonary symptoms, an environmental exposure history, or previous systemic disease. Physical examination and blood tests revealed no remarkable findings. There was no leukocytosis or C-reactive protein elevation. The chest X-ray showed a poorly defined oval opacity in the right lower lung (Figure 1). A chest CT scan revealed an area of ring-shaped consolidation with central ground-glass opacity at the right lower lobe, findings which are classic for the RHS (Figure 2a and 2b). The pathology of a CT-guided lung biopsy of the right lower lung lesion showed chronic inflammatory cell infiltration in the alveolar spaces and bronchioles, as well as organizing intra-alveolar fibroblastic plugs and interstitial inflammation with fibrosis. These findings are typical for OP (Figure 3). COP was diagnosed due to the lack of an infection history, environmental exposure, medication use, or symptoms associated with connective tissue disease. All cultures were negative. The patient was treated with prednisolone 25 mg/day and the lesion resolved after 1 month.

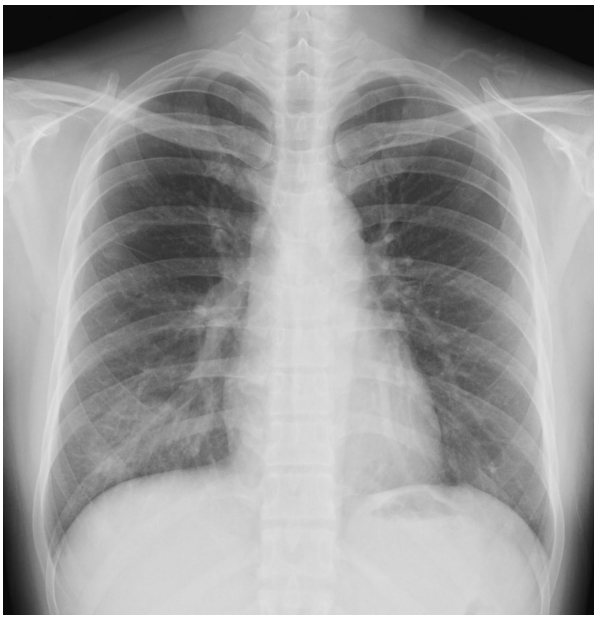

Fig. 1. Chest X-ray showed an oval opacity with central lucency in the right lower lung.

Four months later, the patient developed a non-productive cough without fever, leukocytosis, or C-reactive protein elevation. Chest X-ray showed a ring-shaped opacity at the left lower lung region consistent with RHS again, and recurrent OP was suggested (Figure 4). Intravenous high-dose corticosteroid was given, and then tapered to oral prednisolone therapy. The left lower lung lesion resolved without complication after 1 month of therapy. No further relapses of OP or associated symptoms of connective tissue disease were identified during a 2-year follow-up period.

Discussion

The RHS, also known as the atoll sign, was

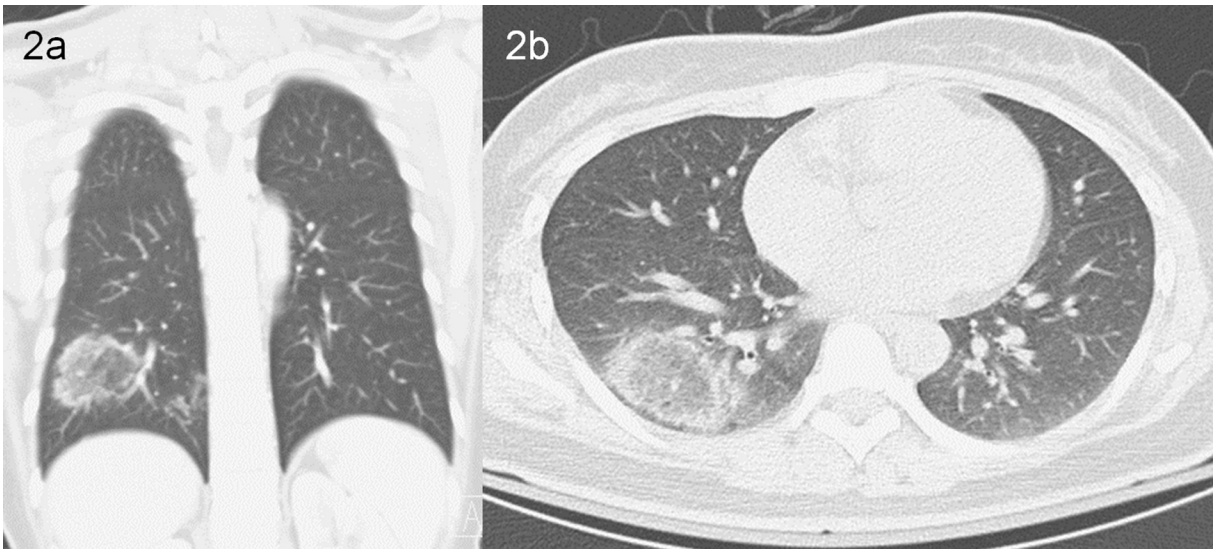

Fig. 2. Chest computed tomography scan of the lung window revealing a 5.6×3.2 cm ring-shaped consolidation with central ground-glass opacity at the right lower lobe, which is a typical reversed halo sign. (a) Coronal section view. (b) Axial section view.

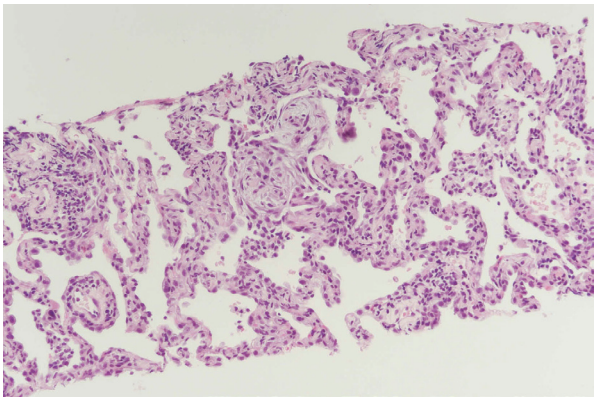

Fig. 3. Pathology of CT-guided lung biopsy showing organizing pneumonia with organizing intra-alveolar fibroblastic plugs and interstitial chronic inflammation. (Hematoxylin and eosin staining, 200x magnification)

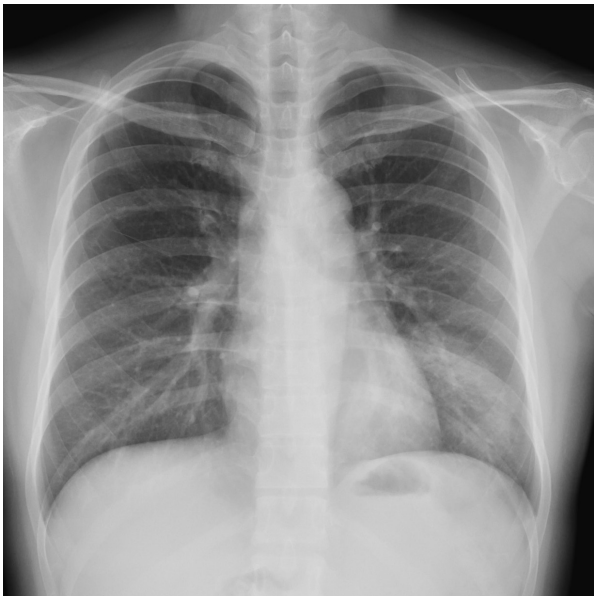

Fig. 4. Chest X-ray showing a ring-shaped opacity at the left lower lung region, favoring recurrent organizing pneumonia with a reversed halo sign.

first reported in a case of COP in 1996. The RHS is defined as a central ground-glass opacity surrounded by a complete or near-complete ring of consolidation on chest CT, resembling a circular coral reef island in the ocean, known as an "atoll" in the Dhivehi language of the Maldives. The sign is rare, and is found mostly in COP, as well as in secondary OP. The RHS was initially thought to be a unique and specific finding for this disease [3-5]. However, an increasing number of cases of RHS have been reported in a variety of other infectious and non-

Table 1. Summary of Published Cases with the Reversed Halo Sign.

Causes	Immune status			
	Immuno- competent	Immuno-compromised*	NA	Total
Noninfectious				
COP[4,6,10,11,13]	28	1	53	82
Secondary OP[4]	15		15	30
Pulmonary embolism[4,12,13]	15		7	22
Vasculitis[6]	2		3	5
Sarcoidosis[6]	3		11	14
Pulmonary edema[4,13]	1		3	4
Lung cancer[+ 4,6,9]	1		19	20
Idiopathic NSIP[4]	2			2
Lymphomatoid granulomatosis[4]	2			2
CEP[8]	1			1
Hypersensitivity pneumonitis[4]	1			1
Tuberous sclerosis complex[4]	1			1
LIP[4]	1			1
Lipoid pneumonia[4]	1			1
Infectious				
Paracoccidioidomycosis[4]			29	29
Pulmonary mucormycosis[4,7]		16	8	24
Invasive pulmonary aspergillosis[4]		1	7	8
Histoplasmosis[4]	1		0	1
Cryptococcus[4,6]			2	2
PJP[4]		1	1	2
H1N1 ARDS[4]	3			3
Tuberculosis[4,6,13]	20		51	71
Legionella pneumophila[4]			2	2
Mycoplasma pneumonia[13]	1			1
Psittacosis[4]	1			1
Total	100	19	211	330

*Cases are grouped according to immune status. Immunocompromised status includes hematologic malignancies, diabetes mellitus, and post-chemotherapy state.

[+] Lung cancer: 19 cases of lepidic-predominant adenocarcinoma, 1 case of primary pulmonary lymphoma.

ARDS: adult respiratory distress syndrome; CEP: chronic eosinophilic pneumonia; COP: cryptogenic organizing pneumonia; LIP: lymphocytic interstitial pneumonia; NA: immune status not available; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; PJP: Pneumocystis jirovecii pneumonia.

infectious pulmonary diseases in recent years [4-5].

A total of 330 cases of RHS have been published in the Pubmed database, including a systematic review by Maturu *et al*., a large-scale study conducted in China by Zhan *et al*., and other case reports (Table 1) [4,6-13]. Overall, the leading cause of RHS is OP (112 cases), followed by tuberculosis (TB) (71 cases), pulmonary fungal infection (66 cases), pulmonary embolism (22 cases), and lung cancer (20 cases). Immune status was indentified in 119 reported cases, of which 100 were immunocompetent. In immunocompetent patients, the most common cause was OP (43 cases), the second most common was TB (20 cases), and the third, pulmonary embolism (15 cases). Only 1 case of fungal infection was reported in the immunocompetent group (histoplasmosis). However, among the 19 immunocompromised patients with RHS, there were 16 cases of pulmonary mucormycosis, 1 case of COP, 1 of invasive pulmonary aspergillosis, and 1 of Pneumocystis jirovecii pneumonia. Of the remaining 211 RHS cases without available immune status information, 68 cases were OP, followed by TB, pulmonary fungal infection, and lung cancer [4,6-13].

Based on the above, immune status is critically important to guiding the differential diagnosis in RHS. For immunocompetent patients, the most likely diagnosis would be cryptogenic or secondary OP. TB is the second most common cause, and therefore plays a major role in the differential diagnosis in endemic areas. Marchiori *et al*. evaluated RHS image features in 12 active pulmonary TB and 10 COP patients. In their study, all 12 TB patients with RHS showed associated nodular walls or nodules within the ring, whereas none of the OP patients with RHS had associated nodular lesions. The authors concluded that the associated nodular lesions were a strong indicator of active pulmonary TB [14]. Pulmonary embolism, lung cancer, and sarcoidosis also account for a small number of RHS cases. Although many reported cases involving the above 3 diseases did not include information regarding patient immune status, these diseases do, in fact, frequently occur in immunocompetent patients [4,6-13].

By contrast, pulmonary fungal infections should be considered first in immunocompromised patients with RHS, and further microbiology work-up with empirical antifungal therapy should be commenced [4,6]. Paracoccidioidomycosis is prevalent only in Latin America, and should be considered only for those living in this endemic area [15]. In regions outside of Latin America, the most common cause of RHS in immunocompromised patients would be pulmonary mucormycosis, and the second, invasive pulmonary aspergillosis. Marchiori *et al*. performed a study to evaluate RHS images in 8 cases of pulmonary mucormycosis, 7 of invasive pulmonary aspergillosis, 10 of COP, and 15 of secondary OP. The authors concluded that a consolidation ring thickness > 1 cm, reticulation within the ring, and associated pleural effusions are strong indicators for the diagnosis of pulmonary fungal infection, and against the diagnosis of OP [16].

In conclusion, although RHS is not as specific as was initially expected, it is still a useful image sign for diagnosing OP, TB, and invasive pulmonary fungal infections. Several clinical and radiological features have been identified to guide the differential diagnosis. For immunocompetent RHS patients without nodular lesions, OP is the most likely diagnosis. For RHS with associated nodular lesions, TB is more likely [4,14]. In immunocompromised RHS

patients, pulmonary fungal infection should be considered first, and among these infections, pulmonary mucormycosis is more common than invasive pulmonary aspergillosis. For those with a consolidation ring > 1 cm, reticulation within the ring and pleural effusion, a diagnosis of invasive pulmonary fungal infection would be more confident [4,16].

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反暈徵表現在原因不明器質化肺炎之個案報告及文獻回顧

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反暈徵為環狀實質化包圍中央毛玻璃陰影的一種電腦斷層影像型態。這是器質化肺炎的一種罕見而特殊的徵象。雖然漸漸有其他疾病也發現反暈徵的型態，器質化肺炎仍佔了大多數。在此我們報告一個切片診斷原因不明器質化肺炎表現典型反暈徵的個案，並做簡短的文獻回顧。反暈徵其他重要的鑑別診斷包括肺結核和肺部侵襲性黴菌感染。免疫狀況與一些影像學相關特徵可以做有效鑑別。肺結核造成的反暈徵總是會合併結節病灶。肺部侵襲性黴菌感染造成的反暈徵則大多發生在免疫功能不全患者，而且和圓環厚度大於 1 公分、內部網狀陰影、及肋膜積水有強烈相關。依據這些規則，反暈徵對於器質化肺炎、肺結核及肺部侵襲性黴菌感染的診斷是非常有用的。*(胸腔醫學 **2017; 32: 238-244**)*

關鍵詞：電腦斷層掃描，原因不明器質化肺炎，反暈徵

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