Asthma Control in Asthmatic Patients Treated for Lung Cancer

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Background: The balance of the Th1 and Th2 immune response plays an important role in the regulation of the immune system and in general health. Tumor bearing hosts are supposed to have a balance shifting to the Th2 pathway, while a favorable Th1 anti-tumor pathway is induced in tumor-resected hosts. The clinical impacts of a tumor-related Th2 environment have not been clearly studied. The present study was conducted to test the hypothesis that non-small cell lung cancer (NSCLC) has an impact on control of asthma, a well-known Th2-predominant inflammatory disease.

Method: Thirty-eight patients with the diagnoses of both asthma and lung cancer were retrospectively enrolled. Patients were divided into two groups according to their response to lung cancer treatment, the responder group (complete regression, partial regression and stable disease) and non-responder group (progression of disease). Asthma control test (ACT) scores were analyzed one year before diagnosis, at the time of diagnosis of lung cancer, and at the time of re-staging after cancer treatment.

Results: All the asthmatics with lung cancer had worsening of their symptoms according to their ACT scores at the time of diagnosis of lung cancer compared to scores in the preceding year (21.6 ± 0.5 vs. 16.5 ± 0.8, n = 38, $p < 0.001$). The ACT scores in the responder group (17.3 ± 5.1) were significantly improved after effective lung cancer treatment (22.1 ± 1.8, n = 18, $p < 0.01$). However, the ACT scores in the non-responder group were even worse after disease progression (15.8 ± 5.0 vs. 11.6 ± 4.2, n = 18, $p < 0.001$).

Conclusion: Our observations indicate that asthmatic patients with acquisition or progression of NSCLC may have worsening of their asthma control status. Those patients with good responses to cancer treatment had improved asthma control. These observations indicate that the Th2 pathway in lung cancer may be a contributing factor in asthma control, another Th2 predominant disorder. More sophisticated clinical and biological investigations are necessary to confirm the role of Th1/Th2 counterbalance in lung cancer in the clinical impact on related immune disorders.

(Chang Gung Med J 2011;34:35-43)

Key words: lung cancer, lung cancer treatment, asthma, asthma control, Th2 predominant disorder

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Received: Feb. 24, 2010; Accepted: Jun. 10, 2010
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The balance of the Th1 and Th2 immune response plays an important role in the regulation of the immune system and in general health.[1-4] Dysregulation of the Th1 and Th2 balance has been implicated in several disorders.[5-9] Clinically, type 1 cytokine-predominant responses should be suspected in any delayed-type hypersensitivity-like granulomatous reaction and in infections with intracellular pathogens, whereas conditions involving hypergammaglobulinemia, increased immunoglobulin E levels, and/or eosinophilia are suggestive of type 2 cytokine-predominant conditions.[5]

Type 2 cytokines, including interleukin (IL)-4, IL-5, IL-6, IL-10, and IL-13, have been implicated in the development of lung cancer.[10-13] With the acquisition of non-small cell lung cancer (NSCLC), there tends to be a shifting of the immune status from Th1 to Th2 at the level of transcription and transduction.[14,15] An elevated level of Th2-type cytokines contributes to cancer escape from host immunosurveillance.[16] In tumor bearing mice, a subset of inflammatory monocytes were identified as myeloid-derived suppressor cells which suppress cytotoxic T cell activity by producing IL-13.[17] A sophisticated mouse model also showed that cytotoxic T lymphocyte-mediated tumor immunosurveillance was suppressed by nature killer T cells through production of IL-13.[18] In addition, murine tumor- associated macrophages are M2 skewed,[19] which are believed to be induced by IL-4 and IL-13.[20] It is not completely understood whether a tumor-induced Th2 mircoenviroment has an impact in human hosts.

Asthma is well known as a Th2 predominant disorder.[21,22] In 1992, Corrigan and Kay proposed a model for the pathogenesis of atopic asthma in which predominantly type 2 cytokine (IL-4 and IL-5) production by T cells in response to allergens or virus antigens led to bronchospasm and bronchial inflammation.[21] In 1994, Kline and Hunninghake emphasized the inflammatory nature of the disease and the predominant involvement of IL-4 and IL-5 in atopic asthma.[23] In mouse models of asthma, pulmonary expression of IL-13 causes significant increases in baseline airway resistance and airway hyperresponsiveness (AHR),[24] characteristics of asthma which are inhibited by blockade of IL-13.[25]

Tumor status may have impact on the Th1/Th2 balance. Ito et al. demonstrated that patients with tumor recurrence after tumor resection had depressed Th1-to-Th2 ratios compared with patients without recurrence.[26] We presumed that progression of the tumor skews the host to a Th2 predominant microenvironment and hypothesized that the tumor status may have an impact on the control of asthma. In this retrospective study, we compared the asthma control status of patients who also had NSCLC between groups classified according to their response to treatment for NSCLC. The impact of tumor status on asthma control was addressed.

METHODS

Subjects

Our study was approved by our institutional review board. The diagnoses of all the patients admitted to our hospital are recorded on an electronic database according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Patients admitted to the hospital from Jan 2004 to Dec 2007 who were diagnosed with both NSCLC and asthma were included in this study. The diagnosis of asthma in each patient enrolled was reviewed and defined according to the Global Initiative for Asthma (GINA) guidelines. Each patient had documented reversible airway obstruction on spirometry (forced expiratory volume in one second/forced vital capacity [FEV1/FVC] < 75% predicted, FEV1 increased > 12% and > 200 ml after inhalation of a short acting β-2 agonist), airway airflow variability on peak flowmetery, or AHR on a methacholine provocation test. Subjects presenting with any of the following exclusion criteria were not included in the study: concomitant malignancy other than lung cancer, autoimmune disorders (e.g., collagen disease), hematology malignancy, immunosuppressive conditions (e.g., acquired immunodeficiency syndrome, organ transplantation), and dyspnea attributed to lung cancer complications or chemotherapy- related complications.

Study design

Data collection

All patients were approached in the same manner and the data collection procedure was the same as that used in filling out the patients' charts. At the time of diagnosis of lung cancer, we collected data on baseline, physiologic, and clinical characteristics, including age, gender, smoking history, atopy (hay

fever, eczema, allergy to foods or medicines), lung cancer histology cell type, staging, Eastern Cooperative Oncology Group (ECOG) performance status, the FEV1, method of steroid administration, and frequency of visits to the emergency room (ER), unscheduled outpatient department (OPD) visits and hospitalizations due to asthmatic exacerbation.

According to current GINA guidelines, we classified asthma control status using the asthma control test (ACT).[27-30] The ACT scores of each patient one year before the diagnosis of lung cancer, at the time of diagnosis of lung cancer and at the first restaging after lung cancer treatment were collected. Moreover, each patient's lung cancer treatment response was recorded as a complete resection (CResec), complete response (CResp), partial response (PR), stable disease (SD) or progressive disease according to the Response Evaluation Criteria in Solid Tumors Group criteria.[31] According to each patient's lung cancer treatment response, the patients were divided into two groups, the responder group (CResec, CResp, PR, SD) and non-responder group (PD).

Statistics

Analyses were carried out using SPSS software (SPSS 13.0 for Windows; SPSS Inc., Chicago, IL, U.S.A.). Comparison of categorical variables was made using the chi-square test for nominal dates when appropriate. Non-parametric interval data were initially analyzed using the Mann-Whitney Test for continuous and ordinal variables. Multiple logistic regression analysis adjusted for age was used to identify the variables that were independently associated with the control level of asthma after lung cancer treatment. Comparisons of ACT scores one year before diagnosis, at the time of diagnosis of lung cancer and after NSCLC treatment were made using the Wilcoxon matched pairs signed-ranks test.

All results were considered to be statistically significant at $p < 0.05$.

RESULTS

Characteristics of patients

From Jan 2004 to Dec 2007, a total of 118 patients admitted to our hospital who matched both the diagnosis criteria for asthma and lung cancer in the hospital data base according to the ICD-9-CM were initially screened for this study. Among these patients, 80 patients were excluded after reviewing their charts, including 42 patients with a diagnosis of obstructive airway diseases other than asthma such as chronic obstructive pulmonary disease, and bronchiectasis; 18 patients with lung masses without tissue proof of lung cancer or who were finally diagnosed with a malignancy other than lung cancer; 3 patients with lung cancer diagnosed long before the observation period; 9 patients with NSCLC treated at another hospital or lost to follow up with insufficient data; 5 patients with a diagnosis of small cell lung cancer; and 3 patients with complicated respiratory symptoms related to lung cancer or lung cancer treatment in which judgment of asthma-related symptoms became difficult. One of the latter 3 excluded patients, had a tumor embolism, one had neutropenic fever with pneumonia, and one died soon after diagnosis before any treatment or evaluation could be offered. In the end, 38 patients were analyzed for asthma control.

The baseline characteristics of all patients, responders and non-responders to lung cancer treatment, at the diagnosis of lung cancer are shown in Table 1. The two groups were similar in most baseline characteristics, including gender, smoking status, atopy, lung cancer histology type, staging, ECOG performance status, method of steroid administration, and FEV1. The responders were younger than the non-responders (65.2 $\pm$ 10.5 year-old vs. 72.7 $\pm$ 8.7 year-old, $p = 0.014$). The mean time between the diagnosis of lung cancer and first restaging post-treatment was similar between the 2 groups (150.7 $\pm$ 60.7 days for the responder group vs. 174.75 $\pm$ 115.5 for the non-responder group, $p = 0.861$).

Asthma control deteriorated at diagnosis of non-small cell lung cancer

The ACT score one year before the diagnosis of lung cancer did not differ between the responder and non-responder groups (23.14 $\pm$ 1.8 vs. 21.06 $\pm$ 2.4, $p = 0.075$, Table 2). All patients experienced a deteriorated ACT score at the diagnosis of lung cancer (21.61 $\pm$ 0.49 vs. 16.47 $\pm$ 0.82, $p = 0.000$, Table 2; Fig. 1). The same extent of deterioration in the ACT score was observed in the responders (23.14 $\pm$ 1.8 vs. 17.28 $\pm$ 5.1, $p = 0.017$) and non-responders groups (21.06 $\pm$ 2.4 vs. 15.75 $\pm$ 5.0, $p = 0.001$).

Table 1. Baseline Characteristics of Asthmatics with Lung Cancer

	Responders to lung cancer treatment (18)	Non-responders to lung cancer treatment (20)	*p* value
Age	65.2 ± 10.5	72.7 ± 8.7	0.014
Gender			0.111
Male	9 (50.0)	15 (75.0)	
Female	9 (50.0)	5 (25.0)	
Smoking status			0.199
Never smoked	9 (50.0)	6 (30.0)	
Current smoker	8 (44.4)	9 (45.0)	
Ex-smoker	1 (5.6)	5 (25.0)	
Atopy	7 (33.3)	11 (50.0)	0.492
Histology			0.800
Adenocarcinoma	9 (50.0)	8 (40.0)	
Squamous	5 (27.8)	6 (30.0)	
Other	4 (22.2)	6 (30.0)	
TNM Staging			0.488
I a-IIIa	9 (50.0)	4 (20.0)	
III b-IV	9 (50.0)	16 (80.0)	
ECOG performance status			0.488
0~2	18 (100.0)	18 (90.9)	
3~4	0 (0.0)	2 (9.1)	
Steroids	11 (61.1)	14 (70.0)	0.120
Inhaled	11 (61.1)	11 (55.0)	
Systemic	0 (0.0)	4 (20.0)	
FEV1 (%)	65.6 ± 25.1	49.0 ± 20.2	0.070

Abbreviations: ECOG: Eastern Cooperative Oncology Group; FEV1: forced expiratory volume in one second.
Qualitative variables are expressed as number and (percentages); quantitative variables are expressed as means ± SD.

Differential asthma control status between responders and non-responders to lung cancer treatment

Differential changes in ACT scores after lung cancer treatment were observed between the two groups. The responder group showed an improvement in asthma control according to their ACT scores after effective treatment for lung cancer (17.28 ± 5.1 vs. 22.11 ± 1.8, $p = 0.001$, Table 2; Fig. 1). In contrast, the non-responder group showed worsening of their ACT scores at the time of disease progression (15.75 ± 5.0 vs. 11.55 ± 4.2 $p = 0.000$). The difference in ACT scores between these two groups at restaging after lung cancer treatment was still eminent after adjustment for age (22.11 ± 1.8 vs. 11.55 ± 4.2, $p = 0.003$).

Around 3 months prior to the time of diagnosis of lung cancer, the responder and non-responder groups had a similar frequency of unscheduled OPD visits, ER visits and hospitalizations due to asthma exacerbation (0.61 ± 0.9 vs 0.70 ± 1.2, $p = 0.737$, Table 2). However, during the 3 months before restaging of lung cancer after treatment, the non-responder group had a much higher frequency of unscheduled OPD visits, ER visits and hospitalizations due to asthma attacks (1.80 ± 2.1). The responder group had no unscheduled OPD or ER visits or hospitalizations due to asthma exacerbation during the same period (0.0 ± 0.0).

DISCUSSION

Studies of patients with cancers have indicated

Table 2. Changes in ACT Scores and Frequency of Asthma AE before and after Cancer Treatment

ACT score	Responder (18)	Non-responder (20)	*p* value	*p* value*	Odds ratio	Confidence interval	
						lower	upper
One year before diag.	23.14 (1.8)	21.06 (2.4)	0.054	0.075	1.684	0.949	2.989
At diag.	17.28 (5.1)	15.75 (5.0)	0.290	0.694	1.029	0.892	1.188
After treatment	22.11 (1.8)	11.55 (4.2)	0.000	0.003	1.984	1.272	3.094
Freq. of asthma AE at diag. of lung cancer	0.61 (0.9)	0.70 (1.2)	0.973	0.737	1.120	0.577	2.174
Freq. of asthma AE after treatment of lung cancer	0.00 (0.0)	1.80 (2.1)	0.000	0.997	0.000	0.000	

Abbreviations: ACT: asthma control test; diag: diagnosis; AE: acute exacerbation; Freq: frequency; *: logistic regression adjusted for age.
Scores are expressed as means (SD).

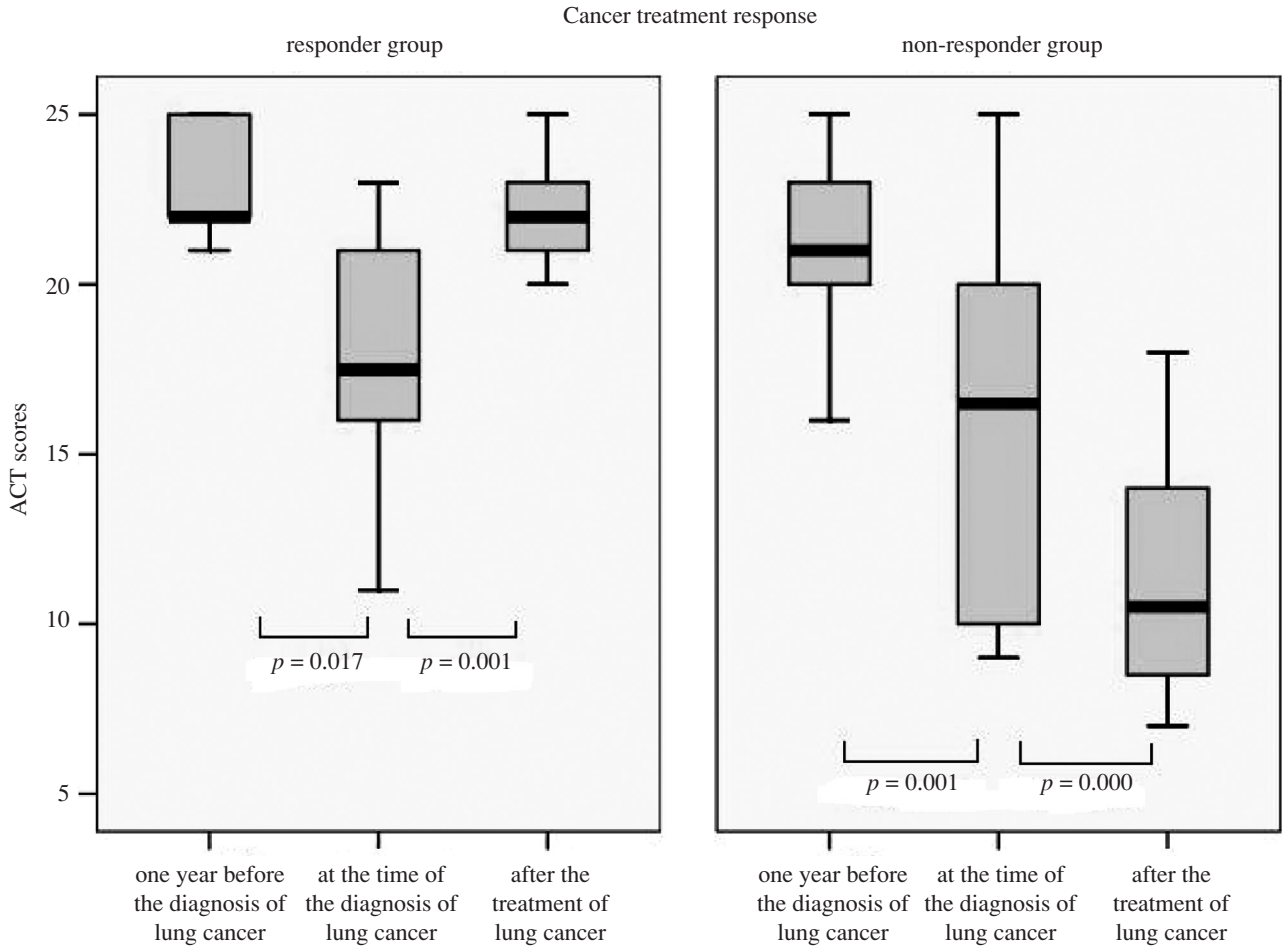

Fig. 1 Comparison of asthma control test scores before and after lung cancer treatment between the responder and non-responder groups. All the results are considered statistically significant, even after Bonferroni adjustment.

that a Th2 cytokine pattern is present at the tumor site, in the peripheral blood lymphocytes and in the tumor-draining lymph node lymphocytes.[6,16,26] Although these cytokines are proposed to inhibit an anti-tumor Th1- and Tc1-dominant pathway and may mediate immunosuppression,[32] their clinical impact has not been clearly demonstrated. In the present study, we investigated the influence of newly diagnosed NSCLC, in which a Th2 cytokine environment is presumed to be present, on asthma in a Th2 concerted condition to address this issue. We found that ACT- defined asthma control was worse when asthmatic patients were diagnosed with NSCLC. The control status of asthma remarkably improved when the underlying lung cancer was effectively treated, while it became worse when cancer progressed.

The Th1 and Th2 immune systems counterbalance each other. It has been well demonstrated by sophisticated murine models that an immune switch toward Th1 inhibits Th2-mediated allergic airway inflammation and hyperreactivity in asthma.[33,34] For NSCLC, switching between Th1 and Th2 seems to be dynamic according to disease conditions. Ito et al reported that the Th1/Th2 ratio in peripheral blood lymphocytes was elevated in patients with early stage NSCLC without recurrence after surgery, while the ratio was significantly depressed in those with tumor recurrence.[26] Our clinical observations seem to parallel these underlying immune conditions. Thus, development of NSCLC may skew the balance

to Th2[6,16,26] and worsen asthma. For responders to lung cancer treatment, who had objectively shrunken tumors, a switch toward Th1 may have counterbalanced the Th2-mediated inflammation and therefore helped to obtain control of asthma. Inversely, progressed NSCLC may have further enhanced the Th2 response, leading to more difficulty in asthma control. Our current study has provided evidence supporting the clinical impact of the NSCLC-mediated Th2 environment on asthma control. There are no current reports on the correlation between the change in ACT scores and the overall Th1/Th2 immune response in bronchial asthma. Our study did not analyze the Th1/Th2 immune status in these patients. However, our findings encourage clinicians to study the mutual immune effects, and the pathophysiological interaction between NSCLC and bronchial asthma.

Although dyspnea due to lung cancer-related complications was excluded in the present study by careful review of clinical presentations and laboratory tests such as chest radiography and computed tomography scans, there may be several alternative explanations to our findings of ACT score changes. First, the primary target organ of both disorders is the lung, and whether there is any influence or interaction is still unknown. Indeed, Gallina et al reported that CD11b+IL-4Rα+ cells in tumor-bearing hosts produce the Th2 cytokine IL-13 and the Th1 cytokine IFN-γ, both in concert triggering the molecular pathways suppressing antigen-activated CD8+ T lymphocytes.[17] This observation challenges the current idea of M2-polarized activation of tumor-associated macrophages, a Th2- related alternative activation of macrophages. Furthermore, difficulty arises from potentially confounding factors that we did not measure. For example, malignancy is considered fatal by the general population. Knowing the progression of a potentially fatal malignant disease is more stressful to the patient and family than knowing that this disorder is under control or even improving.[35] Mental and psychological factors might play an important role in how a patient feels about his dyspnea and general well-being, which may influence symptoms and ACT scores, or even directly worsen the inflammation of asthma via neurogenic inflammation.[36] In addition, the patient's personality, level of anxiety, educational level and economic status, as well as social status, may influence the perception of disease and ACT scores.[37] Although patients in the responder group appeared to be younger than those in the non-responder group, we do not know whether this age difference (65.2 ± 10.5 vs. 72.7 ± 8.7) had any impact on asthma control. Nevertheless, after adjusting for this potential cofounding factor, the difference between those 2 groups was still significant and excluded the effect of the age factor.

The initial frequency of ER and OPD visits and hospitalizations due to asthma exacerbation and the use of medications at the time of lung cancer diagnosis were similar in the two groups (0.61 ± 0.9 vs 0.70 ± 1.2, $p = 0.737$). However, among patients who did not respond to lung cancer treatment, the frequency of hospital visits due to worsening asthma increased. Interestingly, for patients who responded to treatment, there was no such increase. This finding was clinically and statistically relevant before adjustment for age (responder: 0.0 ± 0.0 vs non-responder: 1.80 ± 2.1, $p = 0.000$). Although the p value after adjustment for age was more than 0.05, it could have been due to the small case number in this study.

Our study has limitations which need to be addressed. First, this is a retrospective observational analysis and hence a further prospective trial is needed to confirm the results. Second, the pattern of changes in asthmatic symptoms at the time of lung cancer diagnosis and treatment response, although consistent, should be confirmed in a multicentre study. Third, we need to identify certain specific biological markers or pathophysiologic indicators by which such interactions between NSCLC and asthma can be detected. Fourth, the small sample size limits the possibility to generalize conclusions on the basis of this study. Fifth, we did not take into consideration seasonal influences, geographic or environmental changes, different phenotypes of asthma, or individual factors (personality, mental, social, economic status).

Notwithstanding these important factors, our findings underline the necessity to assess patients with two Th2 predominant disorders, asthma and lung cancer, in order to better understand the response of the immune system to these two disorders. This may help to guide us to discover factors or pathophysiology that affect one or the other disease, or to discover new therapeutic options. Further study will be necessary to directly explore the role of Th2

cytokines in mediating deterioration of asthma control when developing NSCLC or other tumors. In addition, for all patients with cancer even without co-morbid asthma, the impact of Th2 pathways on host health is worth investiging. Finally, our results support a Th2 environment in NSCLC and justify further study into the Th2 pathway as a treatment target directly, or counterbalance of Th1 anti-tumor immunity.

In conclusion, our observations show that asthmatic patients with acquisition or progression of NSCLC have difficulty in controlling asthma symptoms. However, when lung cancer is under control, asthma control also improves. In the context of the current evidence and taking the limitations into account, our findings should prompt physicians to carefully evaluate the factors worsening asthma control and to take the possibility of NSCLC or other cancers into consideration. In addition to known aggravating factors such as allergen exposure, viral infection, environmental factors, occupational factors and emotional factors, underlying NSCLC or other cancers, although rare, may also need to be considered. For asthmatics who also have NSCLC, poorly controlled asthma may be a clinical indicator of NSCLC progression whereas easy control of asthma in a previously difficult case may be an indicator of regression of NSCLC. Whether this observation is due to the counterbalancing between the Th1 and Th2 immune systems needs clarification with more sophisticated clinical and biological investigations.

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哮喘患者罹患肺癌時肺癌治療反應對哮喘控制的影響

謝宗鑫 王圳華 郭漢彬 李岡遠

背 景： Th1 和 Th2 之間的平衡有調節免疫系統和健康的重要角色。腫瘤病患的免疫系統傾向 Th2 之途徑，而病患之免疫系統經由腫瘤切除後會導向具有抗腫瘤功能的 Th1 之途徑。腫瘤誘發的 Th2 環境對臨床上的影響並未被充分的了解。本研究是探討偏向 Th2 免疫環境的非小細胞肺癌對另一個眾所周知的 Th2 爲主的發炎性疾病哮喘之控制的影響。

方 法： 回溯研究 38 例具有哮喘和肺癌診斷患者。患者根據肺癌治療的反應分爲兩組，有反應組（完整切除，完全反應，部分反應和穩定疾病）和無反應組（疾病進展）。本研究記錄患者肺癌診斷一年前，肺癌診斷時，癌症治療後的哮喘控制指數測試 (ACT) 並進行分析。

結 果： 所有哮喘病患跟肺癌診斷一年前相比其 ACT 指數下降（21.6 ± 0.5 與 16.5 ± 0.8，38 例，$p < 0.001$）。在有反應組，其 ACT 指數經有效的肺癌治療後顯著提高（17.3 ± 5.1 與 22.1 ± 1.8，18 例，$p < 0.01$）。但是在無反應組在肺癌進展後 ACT 指數卻變更差（15.8 ± 5.0 與 11.6 ± 4.2，18 例，$p < 0.001$）。

結 論： 哮喘患者罹患非小細胞肺癌或肺癌進展時哮喘控制會惡化。對癌症治療反應良好的病人會有較好的哮喘控制。這些現象支持傾向 Th2 途徑之非小細胞肺癌對哮喘有臨床影響的概念。但仍需要更精密的臨床和生物研究來確認肺癌在 Th1/Th2 平衡的作用對臨床之影響。

(長庚醫誌 2011;34:35-43)

關鍵詞：肺癌，肺癌治療，哮喘，哮喘控制，Th2 顯著的疾病

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受文日期：民國99年2月24日；接受刊載：民國99年6月10日
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