ISSN 1023-9855

胸腔醫學

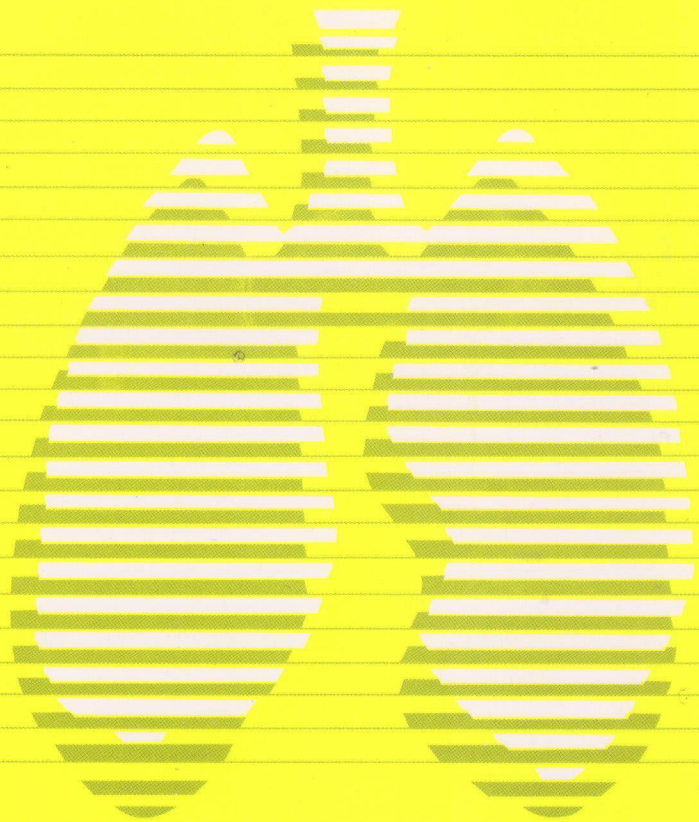
Thoracic Medicine

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

Vol.22 No.2 Apr. 2007

第二十二卷 第二期

中華民國九十六年四月



台灣胸腔暨重症加護醫學會

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No. 1, Sec. 1, Jen Ai Rd., Taipei, Taiwan, R.O.C.

ISSN 1023-9855

中華民國九十六年四月　第二十二卷　第二期
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原著

病例報告

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Orginial Articles

Case Reports

Relationship of Sleepiness, Neck Circumference and Body Mass Index to the Respiratory Disturbance Index among Taiwanese

En-Ting Chang, Guang-Ming Shiao*

Objective: Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive partial or complete upper airway collapse during sleep, and is often associated with hypoxemia and arousal. The disorder not only presents as daytime sleepiness but also induces systemic disease.

Methods: In the study, 477 Taiwanese subjects (males: 380; females: 97), who had visited the Sleep Center at Taipei Veterans General Hospital from 2004 to 2005 because of daytime sleepiness, were enrolled in the study.

Results: The mean age among the tested subjects was 50.3 years. The mean body mass index (BMI) was 26.9 kg/m^2. According to the data, males had a higher body mass index and were sleepier than females in the study. In addition, more severe Respiratory Disturbance Index (RDI) scores were found in the male subjects. Multiple regression analysis, after adjusting for BMI and age, indicated a significant correlation between OSA and the risk factors of BMI, Epworth score, and neck circumference in males. In the female subjects, there was only a correlation between OSA and BMI.

Conclusion: There is a correlation between severity of OSA and BMI, neck circumference and sleepiness in Taiwanese males, but only between severity of OSA and BMI in Taiwanese females. However, females have much more severe OSA than males at a similar BMI and age. ***(Thorac Med 2007; 22: 79-85)***

Key words: sleep apnea, neck circumference, Epworth score, Taiwanese, Taiwan

Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent symptoms of a complete or partial collapse in the upper airway during sleep. OSA is now recognized to be an important health issue in Western countries [1-2]. The characteristics of male gender [3], advanced age, obesity, and increased neck circumference [4] are risk factors for more severe OSA. OSA is an independent risk factor for hypertension [5-7], nocturnal arrhythmias [8], congestive heart failure [9], cerebrovascular disease [10], and metabolic syndrome [11].

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Patients with OSA feel more daytime sleepiness than those in the normal group. In 1991, M. V. Johns had set up the Epworth scale, a well-validated 8-item self-completion questionnaire, to evaluate daytime sleepiness in common situations [12]. The Sleep Heart Health Study (SHHS) indicated that the severity of OSA (defined by the Respiratory Disturbance Index (RDI)) is associated with excess sleepiness (defined by a high Epworth score) in community-dwelling, middle-aged and older adults [13]. Excessive sleepiness has been recognized as an important public problem [14], leading to accidents involving motor-vehicles and at work, impaired social functioning, and reduced quality of life [15]. Most of the study groups have been composed of white and black people, but only 1% of SHHS study groups has been Asian. With the large number of confident studies in Caucasian and African-American groups, we concentrated on the correlation between the risk factors (obesity, male gender, and neck circumference) of OSA and sleepiness in Taiwanese people in Taiwan in this study [16-18].

Materials and Methods

Study Subjects

In this cross-sectional study, 477 adult subjects of Taiwanese (>18 years-old) who had come to our outpatient service at the Sleep Center in Taipei Veterans General Hospital in 2004 and 2005 were enrolled for the study. They accepted a complete overnight polysomnography, and none of the studied subjects had received previous CPAP treatment for OSA. Foreigners and non-Taiwanese were excluded from the study.

Polysomnography

All patients underwent a 1-night polysomnographic study at the Sleep Center in Taipei Veterans General Hospital. Electroencephalogram (C3 and C4), electro-oculogram, chin and leg electromyogram, and electrocardiography (modified V2 lead) (Alice 4) were included in the polysomnographic study. Respiration was monitored as follows: airflow was measured with a nasal cannula/pressure transducer system and a mouth thermocouple, as well as thoracic and abdominal movements (inductive plethysmography), and oxyhemoglobin saturation was measured with finger pulse oximetry. Data collected from the sleep stages were manually recorded according to the international criteria developed by Rechtschaffen and Kales [19]. Those polysomnographic data ranged within at least 6 hours of sleep, in which sleep stage and respiratory event were detected, and were considered acceptable studies with sufficient qualities. According to the parameters of the task force of the American Academy of Sleep Medicine, apnea was defined as a period of breathing cessation, and hypopnea was defined as a 50% reduction in breathing or of a reduction in breathing of less than 50% associated with a 3% desaturation of oxihemoglobin or arousal. These events had to last at least 10 seconds. The AHI was defined as the total number of apneas and hypopneas per hour of total sleep time. In order to exclude post-arousal respiratory events, apneas or hypopneas were not scored if an isolated large breath or movement was immediately followed thereafter. Study subjects in our Sleep Center had taken neither alcoholic nor caffeinated drinks 2 days prior to the study.

Sleepiness

Sleepiness was defined as the Epworth score, a well-validated, 8-item questionnaire. The subject personally rated his or her likelihood to

fall asleep in various circumstances [12, 20]. The range of possible scores was from 0 (the least sleepy) to 24 (the most sleepy). The Epworth score scale was reliable with satisfactory concurrent validation among normal and sleepy Taiwanese [21].

Neck circumference

Neck circumference was measured with a tape at the level of the cricothyroid membrane the night before the polysomnography.

Statistical analysis

Analysis was performed using the SPSS version 10.0 statistical package for Windows (SPSS, Chicago, IL). Data for normal distributions were tested by the Kolmogorov-Smirnov test and homogeneity of variances with Levene's test. Continuous variables were expressed as mean ± SE. The 1-way ANOVA test using the Bonferroni as a post-hoc test was chosen to evaluate physical factors (Age, body mass index (BMI) and neck circumference (NC)) and severity of sleep among the male and female groups. The same experiments were also used to compare the differences among the various subgroups of each group. Age and BMI were considered as the confounding covariates, and each variable of interest (BMI, NC, Epworth score (ES) and (RDI)) used in the comparisons of the demographic table and subgroups were first adjusted for age and BMI by employing the analysis of covariance (the variable BMI was only adjusted for age). Afterward, the derived residuals (adjusted variables) were used for analyses, once the unadjusted data had been examined.

In order to evaluate the relationship among all the variations and the severity of OSA, multiple regression analysis with adjustment for age and BMI were used to evaluate the overall groups of male and female subjects without division into subgroups.

All statistical tests were 2-sided, and *p*-values less than 0.05 were considered to indicate statistical significance.

Results

Four hundred seventy-seven subjects, male (380 subjects) and female (97 subjects) aged over 18 years old, who had visited the Sleep Center at Taipei Veterans General Hospital in 2004 because of daytime sleepiness, were enrolled in the study. The mean (± SD) age of the male adults was 50.1 years old and that of the female adults was 50.9 years old. Male subjects had higher BMI, neck circumference, Epworth score, and RDI, which, with the exception of neck circumference, were significantly different from female (Table 1).

Table 2 shows the relationship of RDI to age, BMI, neck circumference and Epworth score assessed by dividing the subjects into 4 groups of RDI severity, using thresholds commonly employed in clinical practice: Group 1: RDI < 5; Group 2: 5 ≤ RDI < 15; Group 3 : 15 ≤ RDI < 30; Group 4: 30 ≤ RDI < 60; Group 5: RDI ≥ 60. As in the male adults (Table 2-1), the factors of age, BMI, and neck circumference differed significantly by severity of RDI, in relation to the female adults (Table 2-2). However, an increasing Epworth scale score correlated with increasing severity of RDI in male, but not in female, Taiwanese subjects.

Table 3 shows the multiple regression results (*r* value) between RDI and factors associated with OSA. After adjusting for age and BMI, the data still showed a significant difference in BMI, neck circumference, and Epworth score in male adults. However, in female adults, only BMI showed a

Table 1. Demographic data

Characteristic	Male	Female	*p* value
N	380	97	
Age (years)	50.1 ± 15.3	50.9 ± 14.6	0.243
BMI (kg/m^2)	27.0 ± 4.4	26.3 ± 5.7	0.002
NC (cm)	40.2 ± 3.5	35.1 ± 3.4	0.359
ES	8.2 ± 4.6	7.9 ± 5.7	0.013
RDI	27.8 ± 27.2	16.0 ± 23.4	0.001

Data are shown as mean ± SD. BMI: body mass index; NC: neck circumference; ES: Epworth score; RDI: respiratory disturbance index. A $p < 0.05$ revealed a significant difference.

Table 2-1. Clinical and metabolic characteristics of 380 adult male subjects, categorized according to severity of AHI in the study group

Group	Group 1	Group 2	Group 3	Group 4	Group 5	*p* value
N	104	70	63	87	56	
Age (years)	45.5 ± 16.4[4]	50.6 ± 15.1	51.7 ± 15.7	54.4 ± 13.4	49.3 ± 14.1	0.002
BMI (kg/m^2)	26.1 ± 4.0[5]	25.5 ± 3.0[5]	26.6 ± 3.8[5]	26.7 ± 3.5[5]	31.4 ± 5.6	< 0.001
NC (cm)	39.3 ± 3.1[5]	39.4 ± 2.9[5]	39.6 ± 4.0[5]	40.5 ± 2.7[5]	43.3 ± 3.6	< 0.001
ES	8.1 ± 4.6[5]	7.4 ± 4.5[5]	7.6 ± 3.9[5]	7.9 ± 4.5[5]	10.5 ± 4.7	0.001

Data are shown as mean ± SD. BMI: body mass index; NC: neck circumference; ES: Epworth score; RDI: respiratory disturbance index. Group 1: RDI < 5; Group 2: 5 ≤ RDI < 15; Group 3: 15 ≤ RDI < 30; Group 4: 30 ≤ RDI < 60; Group 5: RDI ≥ 60. [1]: $p < 0.05$ against Group 1, [2]: $p < 0.05$ against Group 2, [3]: $p < 0.05$ against Group 3, [4]: $p < 0.05$ against Group 4, [5] : $p < 0.05$ against Group 5.

Table 2-2. Clinical and metabolic characteristics of 97 adult female subjects, categorized according to severity of AHI

Group	Group 1	Group 2	Group 3	Group 4	Group 5	*p* value
N	50	18	13	7	9	
Age (years)	44.9 ± 14.9[2,3]	55.2 ± 10.8	57.9 ± 12.4	53 ± 17.4	55.1 ± 11.2	0.007
BMI (kg/m^2)	24.3 ± 4.5[4]	26.7 ± 4.9	27.9 ± 5.4	27.3 ± 4.5	33.7 ± 7.9	< 0.001
NC (cm)	33.9 ± 3.0[3, 5]	35.0 ± 2.8[5]	36.7 ± 3.5	35.2 ± 3.3	39.2 ± 3.3	< 0.001
ES	7.8 ± 5.6	6.4 ± 5.7	8.9 ± 5.5	6.3 ± 4.2	11.2 ± 7.3	0.273

Data are shown as mean ± SD. BMI: body mass index; NC: neck circumference; ES: Epworth score; RDI: respiratory disturbance index. Group 1: RDI < 5; Group 2: 5 ≤ RDI < 15; Group 3: 15 ≤ RDI < 30; Group 4: 30 ≤ RDI < 60; Group 5: RDI ≥ 60. [1]: $p < 0.05$ against Group 1, [2]: $p < 0.05$ against Group 2, [3]: $p < 0.05$ against Group 3, [4]: $p < 0.05$ against Group 4, [5]: $p < 0.05$ against Group 5.

significant difference to RDI after adjusting for confounding factors. Females had much more severe OSA than males at a similar BMI and age.

Discussion

In our study, male gender was a risk of OSA in Taiwanese, as in Caucasians. Although there were no normal case-control subjects in the study (all subjects in the experiment had "subjectively" felt daytime sleepiness), males tended to have higher Epworth scores and RDI than females, and males had a higher body mass index than females. BMI showed the closest correlation to the severity of OSA. It was considered as a plausibly core problem in the circle of OSA, metabolic syndrome

Table 3. Multiple regression analysis of RDI, BMI, neck circumference and Epworth scores, adjusted for confounding factors

Gender	Male	Female
BMI (kg/m^2)	0.416$^{\#}$	0.488$^{\#}$
NC (cm)	0.105*	0.095
ES	0.113*	0.042

Data are shown as the correlation coefficient (r value) of BMI, neck circumference, and Epworth score to RDI; each variable of interest (BMI, neck circumference and Epworth score) was first adjusted for age and BMI by employing an analysis of covariance (the variable BMI was only adjusted for age). The derived residuals (adjusted variables) were then again used for analyses. RDI: respiratory disturbance index; BMI: body mass index; NC: neck circumference; ES: Epworth score. *: $p < 0.05$, #: $p < 0.005$.

and risk of cardiovascular disease. The female group showed more of a relationship between BMI and RDI. One study showed that obesity may be a less significant risk factor in Asians because the majority of the male Asian patients were non-obese. In this study, the mean BMI (kg/m^2) in the Asian group was significant less at the same RDI (26.6 ± 3.7 in Asians vs. 30.7 ± 5.9 in Caucasians, $p < .001$) [22]. However, according to another study, BMI in the Asian group was 3-4 units lower than in the Caucasian group at the same body fat distribution [23]. The cut-off point of the definition of obesity should be 3 units lower for Asians than Caucasians.

Neck circumference could partly represent the thickness of the soft tissue in the craniofacial profile. Many studies of cephalometry and sleep disorder showed that neck circumference was an independent risk factor of OSA, and indicated that neck circumference was correlated to body mass [24]. However, in our study, neck circumference could be an independent predictor of OSA in Taiwanese males, but not in females. Differences in the neck circumference of Taiwanese females had a stronger relationship with BMI and age than with severity of OSA. In females, the severity of OSA and neck circumference could be predicted by BMI and advanced age [25]. Further investigations of the soft tissue profiles in the neck and RDI in Taiwanese populations are required.

The Epworth score could be used as a clinical tool to evaluate patients who may have OSA and daytime sleepiness [20]. Johns developed the Epworth Score Scale in 1991 with specific reference to activities in the Western lifestyle [21]. However, a study showed that the Epworth score was useful to separate Chinese patients with and without a pathological degree of objective daytime sleepiness [22]. Measurements of RDI and the Epworth score have been known to be imprecise [12]; no good correlation between the Epworth score and RDI was revealed in the study, or in the Sleep Heart Health Study [15, 23]. Male adults can easily detect OSA if they feel daytime hypersomnolence. The Epworth score showed daytime sleepiness in very severe sleep apnea of RDI > 60. The severity of daytime sleepiness in Taiwanese females did not contribute to OSA.

In our study, we used the conventional thermistor for nasal airway flow. A thermistor is a thermally sensitive resistor supplied with a constant but low current. Small temperature changes should produce large resistance changes. The thermistor cannot reliably differentiate between a prolonged inspiration, central apnea and obstructive apnea, compared to nasal pressure recording [26]. Therefore, our airflow data is typically recorded in conjunction with measures of respiratory effort (inductive plethysmography) to minimize recording errors.

In conclusion, there is a correlation between the severity of OSA and BMI, neck circumference and sleepiness in Taiwanese males but only between severity of OSA and BMI in Taiwanese females. Females have much more severe OSA

than males at a similar BMI and age.

References

1. Phillipson EA. Sleep apnea: a major public health problem. N Engl J Med 1993; 328: 1271-3.
2. Strohl KP, Redline S. Recognition of obstructive sleep apnea. Am J Respir Crit Care Med 1996; 154: 279-89.
3. Bixler EO, Vgontzas AN, Lin HM, *et al*. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001; 163: 608-13.
4. Davies RJ, Ali NJ, Stradling JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. Thorax 1992; 47: 101-5.
5. Dart RA, Gregoire JR, Gutterman DD, *et al*. The association of hypertension and secondary cardiovascular disease with sleep-disordered breathing. Chest 2003; 123: 244-60.
6. Pepperell JC, Davies RJ, Stradling JR. Systemic hypertension and obstructive sleep apnoea. Sleep Med Rev 2002; 6: 157-73.
7. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003; 41: 1429-37.
8. Roche F, Xuong AN, Court-Fortune I, *et al*. Relationship among the severity of sleep apnea syndrome, cardiac arrhythmias, and autonomic imbalance. Pacing Clin Electrophysiol 2003; 26: 669-77.
9. Javaheri S. Heart failure and sleep apnea: emphasis on practical therapeutic options. Clin Chest Med 2003; 24: 207-22.
10. Phillips BG, Somers VK. Sleep disordered breathing and risk factors for cardiovascular disease. Curr Opin Pulm Med 2002; 8: 516-20.
11. Ip MS, Lam B, Ng MM, *et al*. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165: 670-6.
12. Johns, MW. A new method for measuring sleepiness: the Epworth sleepiness scale. Sleep 1991; 14: 540-5.
13. Daniel, JG. Relation of sleepiness to respiratory disturbance index. Am J Respir Crit Care Med 1999 Feb; 159(2): 502-7.
14. Mitler, MM, Carskadon MA, Czeisler CA, *et al*. Catastrophes, sleep, and public policy: consensus report. Sleep 1988; 11: 100-9.
15. Leger, D. The cost of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. Sleep 1994; 17: 84-93.
16. Baldwin CM, Griffith KA, Nieto FJ, *et al*. The Association of Sleep-Disordered Breathing and Sleep Symptoms with Quality of Life in the Sleep Heart Health Study. Sleep 2001; 24: 96-105.
17. Redline S, Kump K, Tishler PV, *et al*. Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med 1994; 149: 722-6.
18. Hoffstein V, Mateika S. Differences in abdominal and neck circumferences in patients with and without obstructive sleep apnoea. Eur Respir J 1992; 5: 377-81.
19. Ancoli-Israel S, Klauber MR, Stepnowsky C, *et al*. Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med 1995; 152: 1946-9.
20. Rechtschaffen A, Kales AA, eds. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, DC: Government Printing Office, 1968; National Institutes of Health Publication No 204.
21. Johns, MW Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992; 15: 376-81.
22. Chung KF. Use of the Epworth score scale in Chinese patients with obstructive sleep apnea and normal hospital employees. J of Psychosomatic Research 2000; 49; 367-72.
23. Li KK, Powell NB, Kushida C, *et al*. A comparison of Asian and white patients with obstructive sleep apnea syndrome. Laryngoscope 1999; 109(12): 1937-40.
24. Deurenberg P. Asians are different from Caucasians and from each other in their body mass index/body fat percent relationship. Obesity Reviews 2002; 3: 141-6.
25. Lam B, Ip MS, Tench E, *et al*. Craniofacial profile in Asian and white subjects with obstructive sleep apnoea. Thorax 2005; 60: 504-10.
26. Kapur VK, Baldwin CM, Resnick HE, *et al*. Sleepiness in patients with moderate to severe sleep-disordered breathing. Sleep 2005; 28: 472-7.
27. F Sériès and I Marc. Nasal pressure recording in the diagnosis of sleep apnea hypopnea syndrome. Thorax 1999; 54; 506-10.

嗜睡程度、頸圍與身體質量指數與睡眠呼吸障礙指數的關聯

張恩庭　蕭光明 *

背景：探討嗜睡程度、頸圍與身體質量指數與睡眠障礙指數的關聯。

方法：477 位至門診作睡眠檢查的病患，於做睡眠檢查時同時收集嗜睡程度量表(Epworth score)、頸圍與身體質量指數，經過一晚的睡眠檢查以後，根據這些數值分析其中的關聯性。

結果：受測者平均年齡為 50.3 歲，平均身體質量指數為 26.9 kg/m^2 ，男性比起女性有更高的身體質量指數、嗜睡程度及睡眠呼吸障礙指數。年齡、身體質量指數、頸圍與睡眠嚴重程度相關。若去除掉年齡及體重等影響因素，在男性中，年齡、身體質量指數、頸圍與睡眠障礙嚴重程度相關；而女性只有身體質量指數與睡眠障礙嚴重程度相關。

結論：身體質量指數不管在男性與女性都與睡眠障礙的嚴重程度相關，而在相同的年齡及身體質量指數，女性較男性有更嚴重的睡眠呼吸障礙。*(胸腔醫學* ***2007; 22: 79-85****)*

關鍵詞：睡眠障礙，頸圍，嗜睡程度量表(Epworth score)，台灣人

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Multiple Myeloma Associated with Osteosclerotic Bone Lesion Presenting as Chest Wall Masses

Chih-Hsi Kuo, Hung-Chuan Lin, Chih-Teng Yu, Han-Pin Kuo

Multiple myeloma is a plasma cell neoplasm with osteolytic bone lesion. Osteoblastic bone lesion is rare, and patients frequently present with anemia, renal insufficiency, bone pain and impaired immunity. This report describes the case of a 71-year-old man, who presented with bilateral chest wall masses, but was otherwise asymptomatic. Multiple myeloma with involvement of the ribs was diagnosed via echo-guided biopsy and bone marrow aspiration. The CT showed peripheral and scattered calcification of the mass. The pathology also displayed osteosclerosis manifesting as excess bone deposition on existing bone surfaces, a rare presentation of multiple myeloma with osteoblastic reaction, that should be borne in mind in the presence of diffuse or discrete bone sclerosis. Treatment with conventional chemotherapy rarely achieves complete remission. Autologous stem cell transplantation offers a potential cure. Although rare, multiple myeloma should be included in the differential diagnosis of osteosclerotic bone lesions. ***(Thorac Med 2007; 22: 86-91)***

Key words: multiple myeloma, calcification, osteosclerotic

Introduction

Multiple myeloma (MM) is a disorder of malignant plasma cell proliferation in the bone marrow [1], is associated with monoclonal paraprotein production, and frequently results in anemia, hypercalcemia, and renal function impairment. Patients are vulnerable to infection owing to impaired immunity.

Skeletal involvement led to the hallmark sign of a "punched out" osteolytic lesion [2-4], which is the most common presentation of the bone. However, an osteoblastic lesion may also occur, with an estimated incidence of up to 3% [5]. Either the bone presented with the isolated sclerotic lesion or it was mixed with the osteolytic lesion [6-7], creating confusion among clinicians in diagnosing MM.

This report describes a case of bilateral chest wall masses. The chest PA radiograph and CT clearly demonstrated expansible ribs with peripheral calcification. The diagnosis of MM with sclerotic change was finally established via bone marrow aspiration and echo-guided biopsy from the chest wall masses.

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Case Report

A 71-year-old man experienced progressively enlarging soft tissue masses on the bilateral chest walls over a 1-year period. The masses were firm, non-movable and non-tender, and were located in the left subscapular and right subcostal margins. The patient denied any history of trauma, acupuncture or easy bruising, and was also free of chest pain, chest tightness or dyspnea. The patient had a medical history of hypertension and an old cerebral vascular accident, with the latter having resulted in right lower limb weakness. Physical examination revealed normal a breathing sound, and the cardiac examination was free of cardiomegaly, murmur, or galloping heart sound. The only notable findings were 2 chest wall masses in the left subscapular and right subcostal areas, measuring 5x3 cm and 3x3 cm, respectively. The pulmonary function test showed a mild restrictive pattern. Laboratory hemogram tests demonstrated that there was no anemia (12.2 mg/dl). Moreover, serum biochemistry tests showed elevated total serum protein (8.6 g/dl) and serum calcium level (10.0 mg/dl).

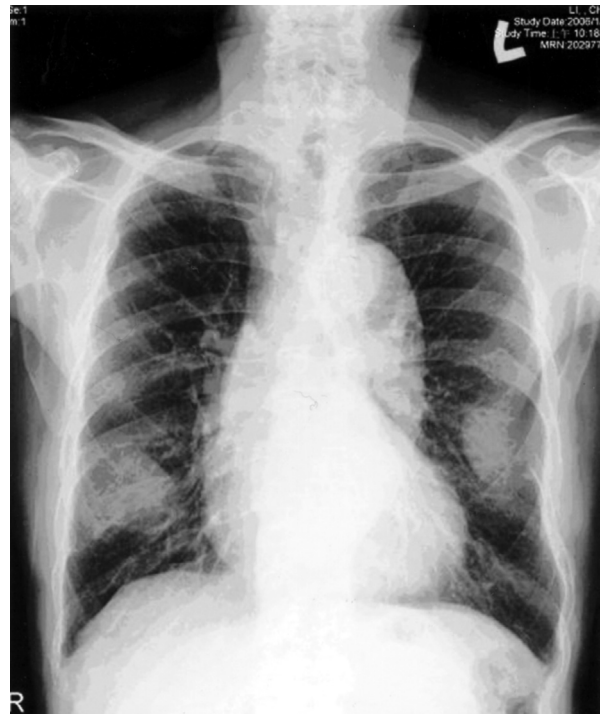

Fig. 1. Two well-defined opacities in the bilateral lower lung field with incomplete borders

Chest PA radiography revealed 2 opacities in the bilateral lower lung field, with round and smooth outlines (Figure 1). The 2 opacities exhibited incomplete border signs, and the adjacent left 8th and right 9th ribs displayed marked expansion. Chest CT indicated that the chest wall

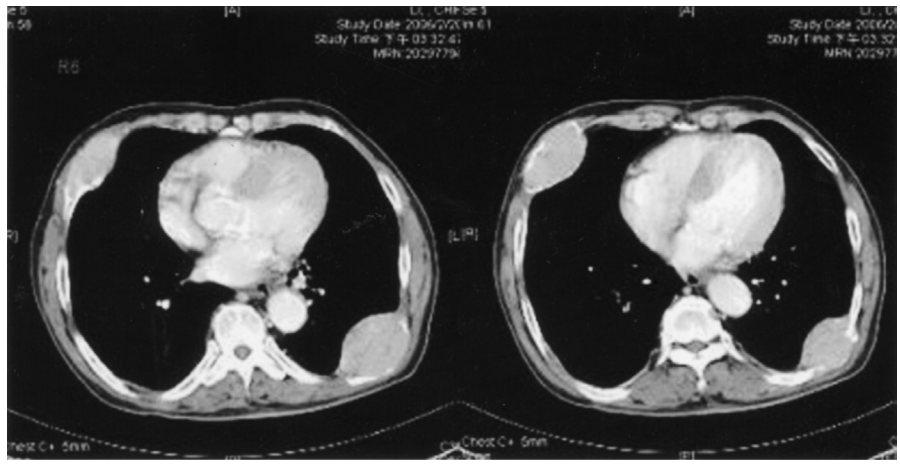

Fig. 2. CT demonstrates the soft tissue masses with enhancement, and adjacent rib expansion

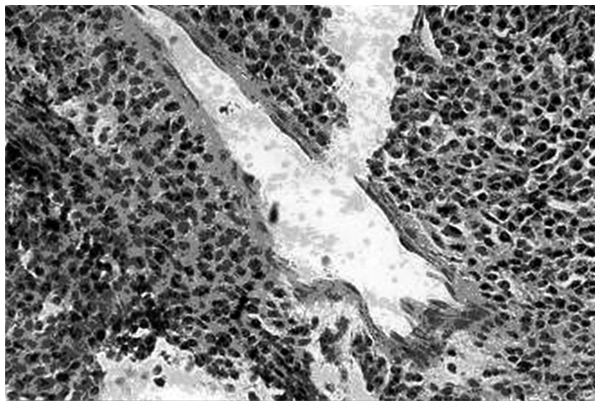

Fig. 3. The pathology shows sheets of the plasmacytoid cell with scattered calcification and osteosclerosis

masses were clearly defined, and were associated with osteoblastic change in the ribs (Figure 2).

Needle biopsy was performed under sonographic guidance, and the pathologist confirmed plasma cell tumor with scattered calcification and osteosclerosis (Figure 3). Bone marrow aspiration obtained from the sternum also exhibited an 87% increase in the proportion of plasma cells, with hypocellular erythroid, myeloid, and megakaryocyte components. Serum protein electrophoresis showed a monoclonal component of IgG immunoglobulin (3,190 mg/dL). Moreover, serum immunoelectrophoresis displayed a spike of IgG kappa chains, with serum β2-microblobulin 4323.6 μg/L and serum albumin 3.4 g/dL. Multiple myeloma International Staging System (ISS) stage II was finally diagnosed, with the osteosclerotic chest wall masses as the initial manifestation. The patient later received conventional chemotherapy with oral prednisolone and mephalan, and continuous outpatient clinical follow up.

Discussion

MM accounts for approximately 1% of all malignancies and approximately 10% of malignant hematological neoplasms [2, 4]. The most common presenting symptoms of MM are fatigue, bone pain and recurrent infection [8]. Around 70% of patients displayed anemia on diagnosis. Hypercalcemia and impaired renal function occurred in 25% and 50% of patients, respectively. M protein is detectable by protein electrophoresis in 82% of patients and by immunofixation test in 93% [8]. The traditional Durie-Salmon staging system was based upon factors correlated with tumor burden, and started to be used in 1975 to classify patients with MM, but has now been replaced by the new International Staging System (ISS) [9]. ISS divides patients into 3 distinct stages based solely on serum β2-microblobulin and albumin levels, better predicts the outcome in MM than the traditional Durie-Salmon staging system, and is of prognostic value. The median survival periods for patients with ISS stages I, II, and III are 62, 44, and 29 months, respectively. Other prognostic factors independent of the ISS system have been introduced by the Mayo Clinic [10]. Patients have been classified as high-risk based on deletion of chromosome 13, hypodiploidy, t (4;14), t (14;16), 17p- and plasma cell labeling index > 3%, and median survival for such patients is less than 2 to 3 years [10]. Meanwhile, patients exhibiting none of the above cytogenetic properties are classified as the standard-risk group.

Multiple myeloma typically involves bone marrow with an osteolytic process, and osteoblastic lesions are rare during the disease course. The osteolytic bone lesion is the most common presentation, and results from osteoclast activating factor (OAF), a cytokine with osteoclast stimulating activity [11]. Recently, the osteolysis has been attributed to an imbalance of osteoprotegerin (OPG) and its ligand RANKL in the bone environment induced by myeloma cells [12]. The

mechanism through which some patients with multiple myeloma do not develop bone loss, or even develop sclerotic bone lesions, remains unclear. A case series involving 10 patients with osteoblastic lesion demonstrated that 90% of these patients had lambda MM [13]. Furthermore, a rare variant of osteosclerotic MM with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions (POEMS syndrome) has been reported to be lambda light chain in the majority [14].

The patient described herein had an atypical course of MM, including not only osteoblastic change of the ribs as an initial presentation, but a lack of clinically evident bone pain, anemia, renal insufficiency or hypercalcemia (at the normal upper limit). The osteoblastic reaction of MM is rare, and should be considered in the differential diagnosis of chest wall masses with sclerotic change.

Generally, up to 60% of patients with MM display a response to conventional chemotherapy with mephalan and prednisolone, and this has been the mainstay treatment for MM [15-16]. However, survival rates with high-dose induction therapy with autologous stem cell transplantation superior to conventional chemotherapy have recently been established [17-18]. Whether the osteosclerotic variant of MM is of a worse prognosis, resistant to chemotherapy, or has characteristic cytogenetic abnormalities, has yet to be determined.

In conclusion, the present case demonstrates the need to consider plasma cell neoplasm in the differential diagnosis of any pattern of bone sclerosis. Though unusual, MM must be considered when confronting bone sclerosis.

References

1. Bataille R, Harousseau JL. Multiple myeloma. N Engl J Med 1997 5; 336(23): 1657-64.
2. The UK Myeloma Forum. Diagnosis and management of multiple myeloma. Br J Haematol 2001; 115(3): 522-40.
3. Moulopoulos LA, Granfield CA, Dimopoulos MA, *et al.* Extraosseous multiple myeloma: imaging features. AJR Am J Roentgenol 1993; 161(5): 1083-7.
4. Rajkumar SV, Gertz MA, Kyle RA, *et al.* Current therapy for multiple myeloma. Mayo Clin Proc 2002; 77(8): 813-22.
5. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 29-1972. N Engl J Med 1972 20; 287(3): 138-43.
6. Driedger H, Pruzanski W. Plasma cell neoplasia with osteosclerotic lesions. A study of five cases and a review of the literature. Arch Intern Med 1979; 139(8): 892-6.
7. Menu Y, Dhermy D, Brousse N, *et al.* Osteosclerotic myeloma. Report on three cases and review of the literature (author's transl). Ann Radiol (Paris) 1981; 24(4): 265-9.
8. Kyle RA, Gertz MA, Witzig TE, *et al.* Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78(1): 21-33.
9. Greipp PR, San Miguel J, Durie BG, *et al.* International staging system for multiple myeloma. J Clin Oncol 2005 20; 23(15): 3412-20.
10. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc 2005; 80(10): 1371-82.
11. Mundy GR, Raisz LG, Cooper RA, *et al.* Evidence for the secretion of an osteoclast stimulating factor in myeloma. N Engl J Med 1974 14; 291(20): 1041-6.
12. Barille-Nion S, Bataille R. New insights in myeloma-induced osteolysis. Leuk Lymphoma 2003; 44(9): 1463-7.
13. Bataille R, Chappard D, Marcelli C, *et al.* Osteoblast stimulation in multiple myeloma lacking lytic bone lesions. Br J Haematol 1990; 76(4): 484-7.
14. Dispenzieri A. POEMS Syndrome. Hematology (Am Soc Hematol Educ Program) 2005: 360-7.
15. Anonymous. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol 1998; 16(12): 3832-42.
16. Sirohi B, Powles R. Multiple myeloma. Lancet 2004 13;

363(9412): 875-87.

17. Attal M, Harousseau JL, Stoppa AM, *et al*. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996 11; 335(2): 91-7.

18. Child JA, Morgan GJ, Davies FE, *et al*. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003 8; 348(19): 1875-83.

以胸壁皮下腫塊表現之骨硬化性多發性骨髓瘤

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多發性骨髓瘤是一種蝕骨性的漿細胞腫瘤，而成骨性病灶是較罕見的。病患常以貧血，腎功能不全，骨頭疼痛及免疫不全來表現。在此我們報告一位 71 歲男性病患，除了兩側胸廓皮下腫塊以外無其他症狀，經過超音波引導切片及骨髓抽吸後診斷為多發性骨髓瘤合併肋骨侵犯。電腦斷層顯示腫塊呈現周邊形散在性鈣化。病理切片亦顯示過多之骨質於骨表面沉積的硬化現象。這是一個多發性骨髓瘤少見的成骨現象，因而遇瀰漫性或散在性之骨硬化時必須特別小心。以傳統化學治療甚少可完全反應；自體幹細胞移植提供治癒的可能性。因此，在遇骨硬化病灶時，仍應將較罕見的多發性骨髓瘤放入鑑別診斷。*(胸腔醫學* ***2007; 22: 86-91)***

關鍵詞：神多發性骨髓瘤，骨硬化，成骨現象

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Malignant Pleural Mesothelioma Presenting with Prolonged Fever and Rapid-Growing Pleural Mass — A Case Report

Po-Sheng Fan, Chiung-Zuei Chen, Wu-Wei Lai*, Tzuen-Ren Hsiue

Malignant pleural mesothelioma (MPM) is an uncommon, but no longer rare cancer. The most common symptoms include dyspnea, chest pain, and unilateral pleural effusion. However, prolonged fever has not been mentioned in published reports. There are several diagnostic means of evaluating pleural effusion, including effusion cytology, pleural biopsies, percutaneous computed tomography (CT)-guided cutting biopsy, and thoracoscopic biopsy. We report a 29-year-old male patient who developed left-side pleural effusion and prolonged fever without an accurate diagnosis until repeated thoracoscopic biopsies were done. MPM was diagnosed, and spread rapidly within 1 month. He died of multiple metastasis 5 months after diagnosis and left pneumonectomy. To the best of our knowledge, this may be the first report of MPM mainly presenting with prolonged fever and a rapidly-growing pleural mass. Hence, mesothelioma should be considered when fever and a rapidly-growing pleural mass occur simultaneously. ***(Thorac Med 2007; 22: 92-97)***

Key words: malignant pleural mesothelioma, prolonged fever, rapid-growing pleural mass, thoracoscopic biopsy

Introduction

MPM is an uncommon, but no longer rare cancer. Unfortunately, the treatment for MPM is deprived and the prognosis is extremely poor. The likelihood of survival over 1 year after diagnosis is less than 50%, and the response to treatment is disappointing. The initial presentation of MPM is usually unilateral pleural effusion associated with dyspnea and chest wall pain [1]. According to the literature, prolonged fever is not a common symptom. The progressive growth of the lesion is also seldom mentioned.

We report a 29-year-old man with an initial presentation of fever and chest pain for 2 weeks. A CT-diagnosed pleural mass grew rapidly within 1 month, and the fever also persisted. To the best of our knowledge, this may be the first report of MPM mainly presenting with prolonged fever and a rapidly-growing pleural mass.

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Case Report

A 29-year-old male who worked in a factory that used organic solvents, such as methylbenzene, experienced chest pain and intermittent fever for 2 weeks. His past history included asthma, and he was a former smoker with a habit of about 1 pack per day for 5 years. The fever occurred often at night and subsided later without chills or cold sweating. The chest pain localized at the left anterior-lower chest wall and was aggravated with deep inspiration. The pain did not radiate to back and was not related to effort. There was mild shortness of breath during effort without orthopnea or paroxysmal nocturnal dyspnea. He denied cough or hemoptysis. Decreased appetite was also noted during the 2 weeks. He visited the local medical hospital where left-side pleural effusion was found. (Figure 1A) The initial pleurocentesis revealed bloody exudate pleural effusion, lymphocyte predominant (72%) without malignant cells. Abrams biopsy was performed 7 days later; however, no definite result was obtained. At the same time, spiking fever without chills and poor appetite also developed. Because no definite diagnosis was made after a 2-week survey, he was referred to our hospital for further evaluation and management.

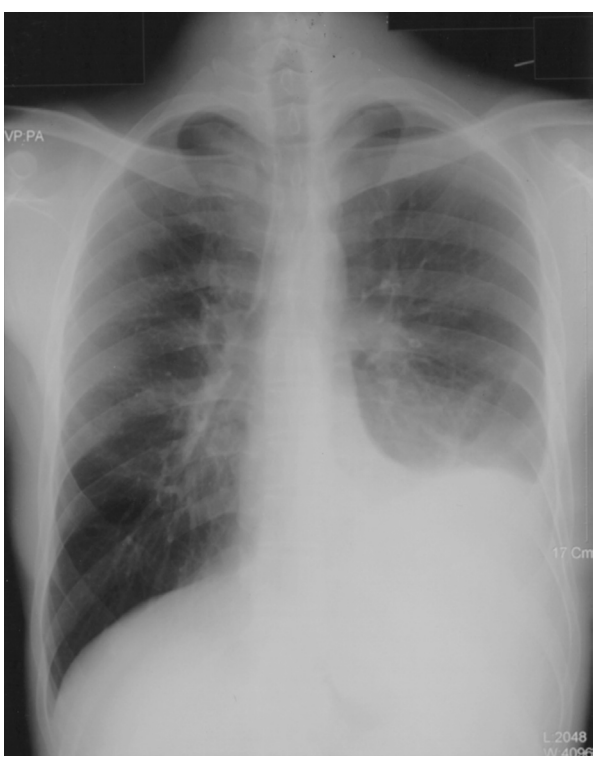

Fig. 1A. Initial chest radiograph showing left-side pleural effusion.

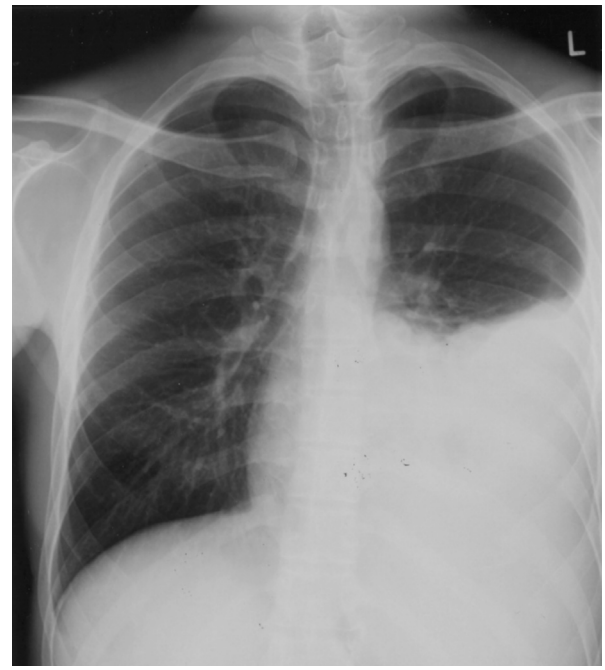

Fig. 1B. Later, the chest radiograph revealed more left-side pleural effusion.

On admission, physical examination revealed a well-nourished, well-developed and febrile patient, whose body weight was 65 kg and height was 183 cm. The chest was symmetrical, and there were decreased breathing sounds in the left lower lobe area without wheezing. There was no clubbing, cyanosis or peripheral lymphadenopathy. An increasing amount of left-side pleural effusion was found on chest radiography (CXR) (Figure 1B). The chest computed tomography (CT) revealed left pleural effusion with a heterogeneous dense lesion (Figure 2). A thoracoscopic

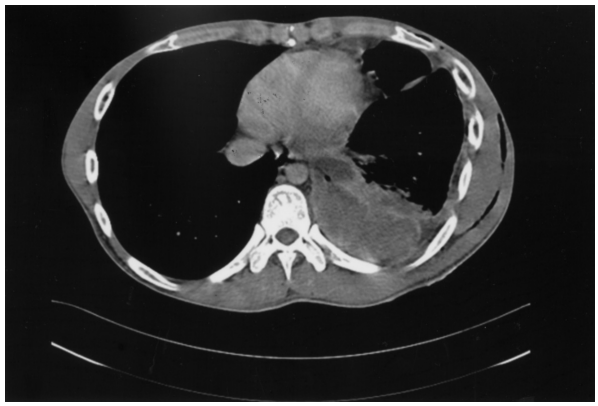

Fig. 2. Chest CT scan showing focal atelectasis of the left lower lobe with a left-side pleural mass of heterogenous density.

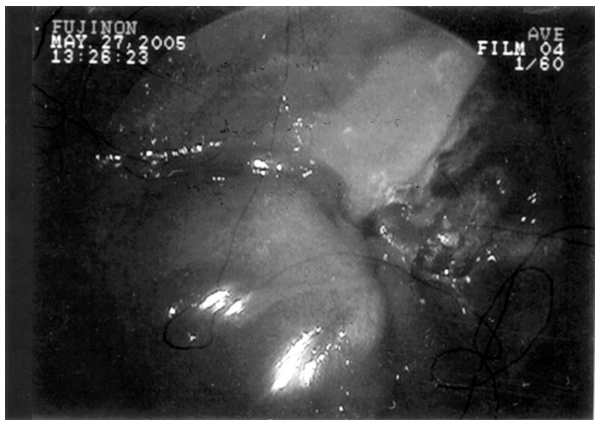

Fig. 3. The left lower lobe was adhesive to the chest wall with costophrenic angle necrotic tissue.

biopsy was performed after consulting the chest surgeon. Diffuse parietal pleural congestion with 3500 ml of bloody pleural effusion was noted. The left lower lobe was adhesive to the chest wall with costophrenic angle necrotic tissue. (Figure 3) The pathologic diagnosis of the biopsy was hemorrhage with fibrosis, and the pathological finding revealed proliferative mesothelial cells infiltrated by neutrophils. Some mesothelial cells displayed enlarged hyperchromatic nuclei. Hemorrhage with hemosiderin-ladin macrophages was found, so trauma-induced hematoma with infection was considered. Fever persisted, even with antibiotics treatment with piperacillin and sulbactam to cover nosocomial infection. No specific bacterial pathogen was isolated; therefore, we changed the antibiotics to levoflocacin for possible drug fever. The possibility of autoimmune diseases and adrenal insufficiency was excluded after serial surveys. After obtaining negative findings in the whole body Gallium inflammation scan, we discontinued all antibiotics and gave him low-dose prednisolone (0.5mg/kg/day). The fever seemed to be relieved and his condition was somewhat better, hence he was discharged after a 3-week hospitalization.

During the next 2 weeks, intermittent fever occurred, combined with decreased appetite. Shortness of breath disturbed him and made him intolerant to ordinary daily work. Admission for further evaluation was suggested at this time. The chest CT showed an enlarged heterogenous lesion, about 12 x 9 x 21 cm in size, compared with the initial size of 8 x 4 x 12 cm about 1 month previous, in the left pleural space, with compression atelectasis of the left lung. There was fluid accumulation in the pericardium and contralateral pleural space (Figure 4). Percutaneous CT-guide biopsy was carried out with an 18-gauge needle, but there was not enough tissue for the definite diagnosis. Because of the lack of an accurate diagnosis and the progressively worsening condition, the patient finally accepted repeated thoracoscopic examinations 2 weeks after admission. The frozen pathology revealed malignant mesothelioma that exhibited an epithelioid and spindle-like appearance. Left pneumonectomy was performed on the same day, with lymph node dissection. He received radiotherapy and palliative chemotherapy with cisplatin and pemetrexed during the next 4 months. Five months later, the patient died of malnutrition and multiple metastases which is including liver,

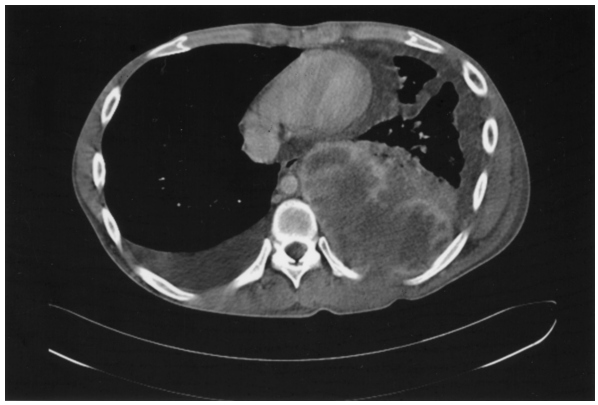

Fig. 4. Chest CT scan showing an enlarged heterogenous lesion in the left pleural space with compression atelectasis and fluid accumulation in the mediastinal pleura and contralateral pleural space.

peritoneal carcinomatosis, peripancreatic, perigastric and intraperitoneum lymphadenopathy, and contralateral pleural space.

Discussion

The incidence of MPM is associated with asbestos usage. Although there is no satisfactory treatment for MPM, an accurate diagnosis is important due to its extremely poor prognosis. Typically, a patient with mesothelioma presents with pleural effusion, which is often associated with chest wall pain, dyspnea, and cough. Constitutional symptoms such as weight loss and fatigue can be present, but are usually found in the later course of the disease, and may be related to a poor prognosis [2-3]. Furthermore, fever is seldom mentioned in relation to MPM, and the speed of its spread has not been described in the literature.

Our patient was a young male without evidence of asbestos exposure. He had the common early symptoms of mesothelioma with unilateral pleural effusion, chest pain and dyspnea. However, prolonged fever, lasting about 2 months, occurred without definite etiology. Moreover, to date, no one has reported fever as the initial presentation of MPM.

Based on the pleural effusion analysis, tuberculosis pleurisy, or malignancies such as lung cancer or metastasis, were considered. The initial bloody pleural effusion puzzled us and interfered with further management.

The common causes of fever of unknown origin include infections, neoplasms, systemic rheumatologic or vasculitic diseases, drug-related fever, adrenal insufficiency, and others. Based on the above examination results, we excluded the possibility of fever of unknown origin, except tumor fever.

Pleural effusions are initially investigated by thoracocentesis to make the diagnosis of MPM. The percentage of accurate diagnoses based on the pleural effusion cytology was very low (26%) in a past report [4]. In the presence of pleural effusion, a blind pleural biopsy can be performed with a reverse bevel needle. The sensitivity may increase to 21-43% for the detection of MPM [5]. Image-guided percutaneous cutting needle biopsy of thickened pleura was reported with 86% sensitivity for detection of MPM [6]. Thoracoscopy is frequently used for accurate diagnosis of MPM because of the large, visually guided biopsy samples. Although the cost and anesthetic risks are concerns, thoracoscopy is a safe and highly sensitive (up to 98%) method for the diagnosis of malignant pleural disease [7].

The TNM-based staging system for mesothelioma is based on surgical and pathologic findings, but is potentially applicable to radiographic staging by CT scan; it also provides prognostic value [8]. There are 3 histologic types of mesothelioma—epithelial, mixed, and sarcomatous. The epithelial subtype is considered to have the best prognosis, and sarcomatous is said to be the worst. But the overall prognosis for all patients is very poor. Most large series report a median

survival time of 8-12 months from the time of diagnosis [9]. Some studies have reported that poor performance status, high leukocyte count, and male gender are poor prognostic factors.

One study reported the results of treatment in 183 patients with extrapleural pneumonectomy followed by radiation and intravenous chemotherapy [10]. Those with an epithelial cell type, clear margins post-resection and negative lymph nodes had a 2-year survival rate of 68%. But patients with sarcomatous or mixed cell types fared poorly, with a 2-year survival rate of 16% [10]. In our case, although the thoracoscopic biopsy was done, the pathologic finding did not support the diagnosis we considered initially. We thought that the disease was trauma-related hemorrhage and drug fever. After 1 month of empiric therapy, the lesion size progressed and the symptoms persisted. The final pathology was confirmed after the second thoracoscopic biopsy. The further treatment response was poor and was compatible with the literature review. The survival time after diagnosis was lower than the median survival time.

In conclusion, prolonged fever and pleural effusion may be related to many etiologies, including MPM. If there are pleural effusion with an uncertain etiology and a bizarre clinical course, such as prolonged fever and a rapidly-growing pleural lesion, early thoracoscopic intervention is necessary.

References

1. Adams VI, Unni KK, Muhm JR, *et al.* Diffuse malignant mesothelioma: diagnosis and survival in 92 cases. Cancer 1986; 58: 1540-51.
2. Scott B, Mukherjee S, Lake RA, *et al.* Malignant mesothelioma. In: Hanson H ed. Textbook of Lung Cancer. London; Martin Dunitz 2000; 273-93.
3. Yates DH, Corrin B, Stidolph PN, *et al*. Malignant mesothelioma in southeast England: Clinicopathological experience of 272 cases. Thorax 1997; 52: 507-12.
4. Ruffie P, Feld R, Minkin S, *et al.* Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. J Clin Oncol 1989; 7: 1157-68.
5. Achatzy R, Beba W, Ritschler R, *et al.* The diagnosis, therapy and prognosis of diffuse malignant mesothelioma. Eur J Cardiothorac Surg 1989; 3: 445-7.
6. Adams RF, Gray W, Davies RJ, *et al.* Percutaneous image-guided cutting needle biopsy of the pleura in the diagnosis of malignant mesothelioma. Chest 2001; 120: 1798-802.
7. Menzies R, Charbonneau M. Thoracoscopy for the diagnosis of pleural disease. Ann Intern Med 1991; 114: 271-6.
8. Rusch VW, Venkatraman E. The importance of surgical staging in the treatment of malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1996; 111: 815-25.
9. Curran D, Sahmoud T, Therasse P, *et al*. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer Experience. J Clin Oncol 1998; 16: 145-52.
10. Sugarbaker DJ, Flores RM, Jaklitsch MT, *et al.* Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999; 117: 54-63.
11. Boylan AM. Mesothelioma: new concepts in diagnosis and management, Curr Opin Pulm Med 2000; 6: 157-63.
12. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma, Lancet 2005; 366: 397-408.

以發燒及快速生長之肋膜腫瘤爲表現之惡性肋膜間皮瘤—病例報告

范博勝　陳炯睿　賴吾為*　薛尊仁

惡性肋膜間皮瘤是個不常見卻又不再罕見的癌症。常見的表現包括有胸痛、呼吸困難、及肋膜積水。但發燒並不是惡性肋膜間皮瘤的典型臨床表現。一般來說有幾種方法可以用來評估肋膜腔積液：包括肋膜腔液抽吸細胞學檢查、肋膜切片、經皮電腦斷層導引下肋膜切片以及胸腔鏡切片。

本例我們報告一位29歲男性病例以左側肋膜積液合併發燒及左側胸痛來表現。經過細針抽吸及肋膜切片皆無確切診斷，之後接受胸腔鏡切片描述為慢性發炎組織以及創傷後造成的血腫。一個月後，該病例仍因持續發燒以及全身倦怠合併喘的情形再次進行評估，再一次的胸腔鏡切片證實為惡性肋膜間皮瘤。經過左側全肺切除，局部放射線治療及化學治療後，該病例在五個月後因全身多處轉移死亡。因此當臨床表現為發燒及快速生長之肋膜腫瘤時，惡性肋膜間皮瘤是需要被考慮的診斷之一。因為其癒後極差,因此正確且即時的診斷更形重要。*(胸腔醫學* ***2007; 22: 92-97****)*

關鍵詞：惡性肋膜間皮瘤，發燒，快速生長之肋膜腫瘤，胸腔鏡切片

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Mucinous Bronchioloalveolar Carcinoma: A Case Report and Literature Review for Immunohistochemical Evaluation and Prognosis

Chung-Yu Chen, Yih-Leong Chang*, Kuan-Yu Chen, Yung-Chie Lee**, Pan-Chyr Yang

Mucinous bronchioloalveolar carcinoma (BAC) is an uncommon histologic type of lung adenocarcinoma. The various clinical, radiographic and pathologic findings of different subtypes of BAC are correlated with survival. The mucinous type of BAC histologically mimics other primary mucin-producing adenocarcinomas of the lung and metastatic mucinous adenocarcinomas. Commonly-used immunohistochemical markers, such as thyroid transcription factor-1 (TTF-1), cytokeratin (CK) 7 and CK20 are helpful in distinguishing between primary pulmonary adenocarcinoma and metastatic adenocarcinoma. Therefore, subclassification of lung adenocarcinoma by immunohistochemical evaluation will probably help in establishing diagnoses and predicting survival. We report a 68-year-old female patient with mucinous BAC that initially manifested as a focal opacity in the right lower lobe on chest radiography. Right lower lobe lobectomy and lymph node dissection were performed. The post-operation course was smooth, and she has been followed at our clinic without recurrence, as of this writing. The literature concerning immunohistochemical studies and prognosis are reviewed. ***(Thorac Med 2007; 22: 98-105)***

Key words: bronchioloalveolar carcinoma, immunohistochemistry, cytokeratins, thyroid transcription factor

Introduction

Bronchioloaveolar carcinoma (BAC) is an uncommon histologic type of lung cancer [1]. The mucinous subtype of BAC is even rarer, in comparison with other subtypes of BAC [2]. The mucinous subtype, in particular, histologically mimics other mucin-producing adenocarcinomas of the lung and mucinous adenocarcinomas originating from other sites, such as the gastrointestinal tract. Differentiating primary pulmonary adenocarcinoma from adenocarcinoma metastatic to the lung is a common diagnostic problem, especially challenging in BAC. Immunohistochemical analysis is a useful adjunct for ascertaining the site of origin in such cases.

The most commonly used immunohistochemical markers for discriminating primary pulmo-

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nary adenocarcinoma from metastatic adenocarcinoma are cytokeratin (CK) 7, CK20, and thyroid transcription factor-1 (TTF-1) protein [3-7]. The majority of conventional pulmonary adenocarcinoma is immunoreactive for antibodies against TTF-1 and CK7, and negative for CK20. However, several investigators have shown that mucinous and nonmucinous BACs have different immunohistochemical staining patterns [8-14].

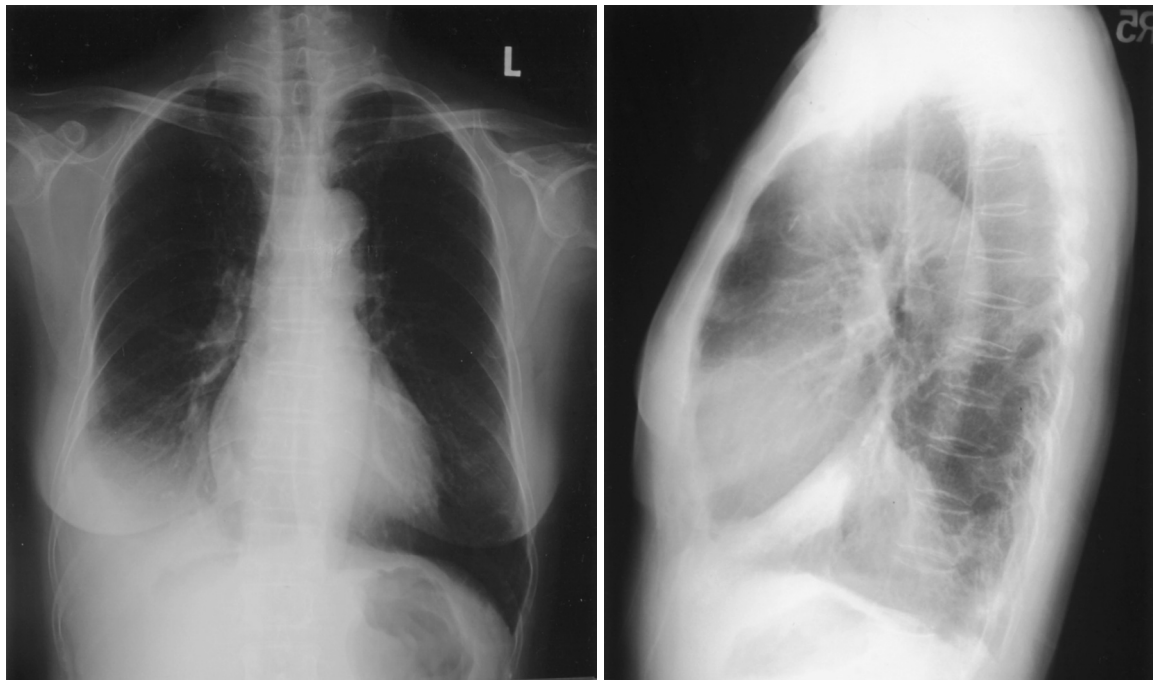
In general, BAC has a better prognosis than other histologic types of primary lung cancer [2]. Various clinical, radiographic and pathologic presentations have been claimed to be associated with survival. Herein, we report a case of mucinous BAC. Right lower lobe lobectomy and lymph node dissection were performed. The previous literature is also reviewed for immunohistochemical evaluation and prognostic factors.

Case Report

A 68-year-old woman was referred to our clinics for chronic cough and right lower lung opacity in the chest radiograph. She had had hypertension for 3 years and received regular medication in a local clinic. She began suffering from cough with white sticky sputum 1 year ago. There was no fever, dyspnea, exertional dyspnea, hemoptysis, chest pain, or chest tightness. Without medication, the cough became aggravated with increased sputum production in May 2005. She went to a local hospital, where chest radiography revealed a right lower lobe consolidation, but the sputum smear revealed no pathogen. Lung biopsy was suggested, but the patient refused. After that, she took alternative medication for 3 months, but the chronic cough persisted. She came to our hospital for further examination in October 2005.

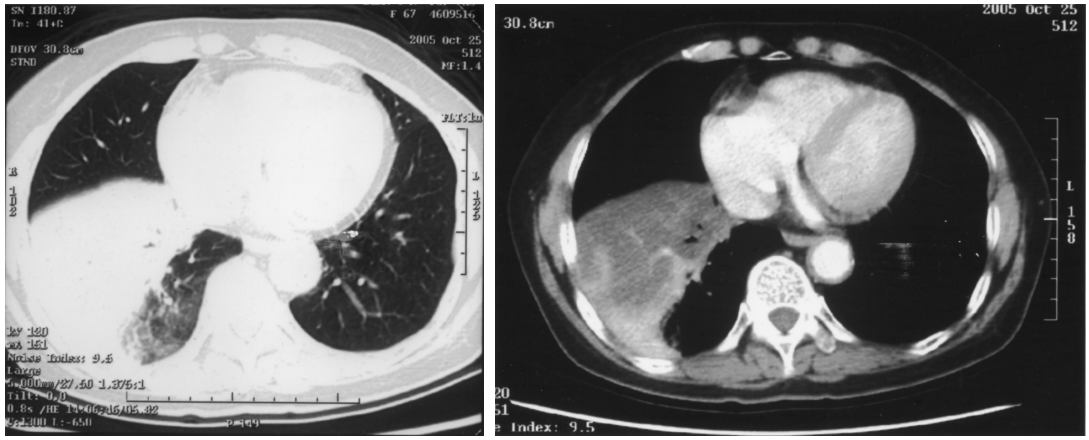
Her body temperature was 36.8^{o}C, pulse rate was 62/min and respiratory rate was 20/min. Blood pressure was 120/80 mm Hg. The patient's general appearance was well developed. An initial physical examination by auscultation disclosed decreased breathing sounds in the right lower lung field. Laboratory investigations revealed leukocytosis (white blood cell count 11950/mm^3). Biochemical studies and electrolytes were all within normal range. The chest radiography demonstrated a focal opacity with air bronchograms in the right lower lobe associated with mild pleural effusion (Figure 1). Chest computed tomography showed consolidation in the right lower lobe. No definite soft tissue density or tumor lesion was found (Figure 2). Bronchoscopic examination showed no obvious endobronchial lesion. Washing cytology, cultures and acid-fast bacteria smear were all negative. Chest ultrasound revealed a consolidation at the right lower lobe without pleural effusion. Transthoracic sonoguided biopsy for the consolidation was performed. The pathologic examination revealed adenocarcinoma. There was no evidence of distant metastatic lesion on the whole body bone scan and positron emission tomography (PET) scan, except multiple focal areas of hypermetabolism in the right lower lung field.

She was referred to the chest surgeon, and underwent right lower lobe lobectomy with lymph node dissection. Histologically, the tumor showed monotonous proliferation of well-differentiated mucinous epithelium growing along the alveolar walls in a lepidic fashion, with an abrupt transition from tumor to normal alveolar walls (Figure 3). Pleural effusion cytology was negative. A diagnosis of bronchioloalveolar carcinoma with mucin production was made. The tumor cells were immunoreactive to thyroid transcription factor-1 (TTF-1) protein and cytokeratin 7 (CK7), but negative for CK20.



(A) (B)

Fig. 1. Radiographs of the Chest. Posterioranterior (Panel A) and right lateral views (Panel B) of the chest radiography show air space consolidation at the right lower lung field with right pleural effusion.



(A) (B)

Fig. 2. Computed Tomography. Focal opacity with air bronchograms in the right lower lobe is noted (Panel A). No definite soft tissue tumor is found in the right lower lobe or right hilum (Panel B). There is no definite lymphadenopathy in the mediastinum, paratracheal or subcarinal region.

There was no metastasis of lymph nodes. The post-operation course was smooth and she was discharged in November 2005. She was followed at our clinic and there has been no evidence of recurrence up to this writing.

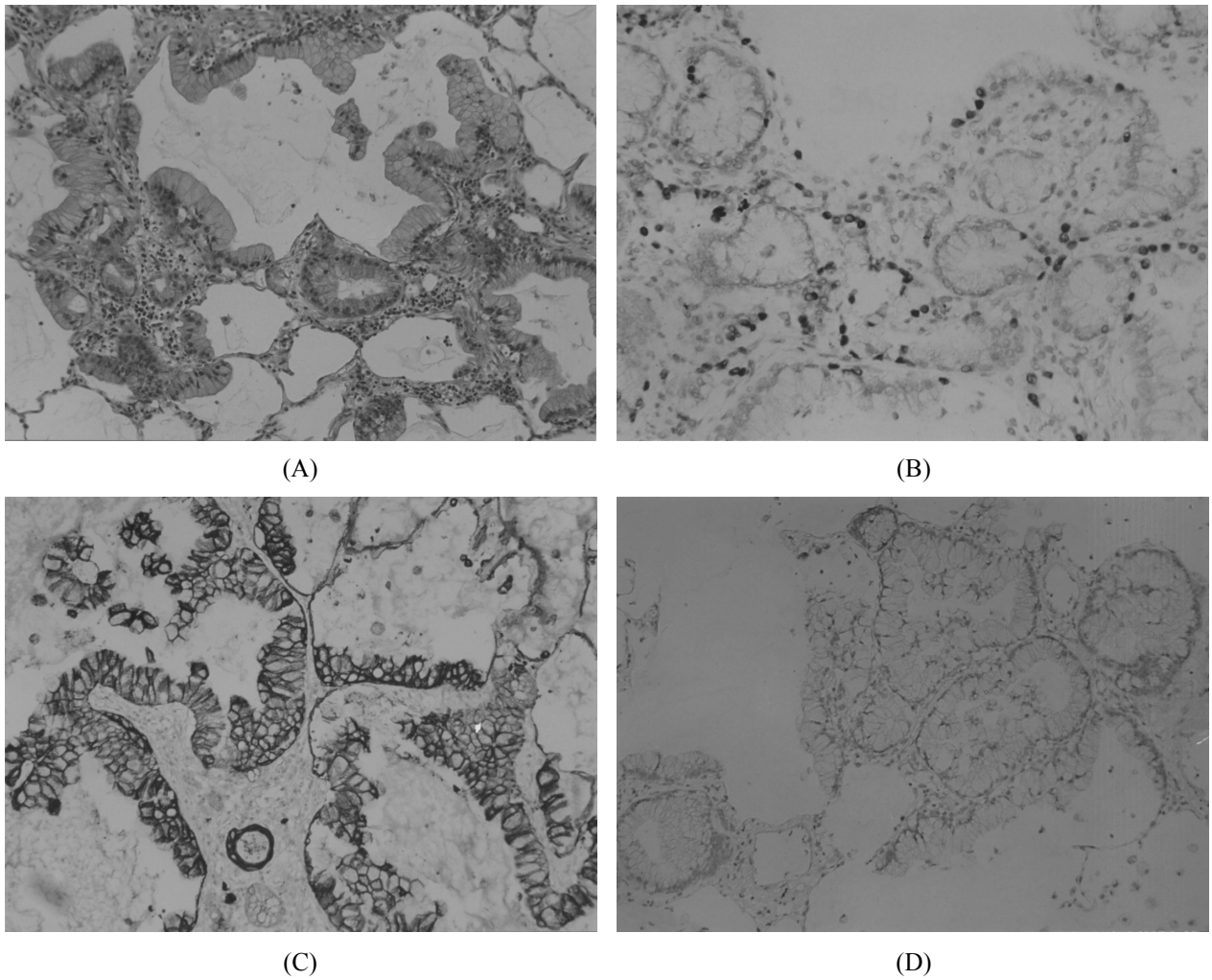


Fig. 3. Immunohistochemical studies of the lung cancer specimen. Microscopically, the tumor is composed of columnar cells resembling goblet cells that proliferate along the framework of the alveolar septae. Mucin production with mucus pooling in the surrounding alveolar spaces is noted (Panel A). The tumor consists of less of an increase in atypical cells invading the adjacent alveolar tissue, which differs from solid adenocarcinoma with mucin formation. In addition, there are no scattered clusters of tumor cells within the pools of mucin, as seen in mucinous (colloid) adenocarcinoma. Positive immunohistochemical staining for TTF-1 (Panel B) and CK7 (Panel C), but negative for CK20 (Panel D), are shown.

Discussion

Bronchioloalveolar carcinoma (BAC) is the least common type of bronchogenic carcinoma, occurring variously from 1% to 9%, with women accounting for 40% of BAC in 1 report [1]. In another series, mucinous carcinoma accounted for 0.24% of all lung cancers [15]. BAC is classified into different histologic subtypes (mucinous, nonmucinous and mixed) [16], which demonstrate a noninvasive pattern and a better prognosis. Adenocarcinoma is the major histologic type of lung carcinoma (52.5%) in Taiwan, and a significant trend toward an increase in adenocarcinoma among men and woman has been noted [17]. The increase in the diagnostic rate of BAC would contribute to a high incidence of adenocarcinoma [18-19].

Mucin-producing adenocarcinoma of the lung comprises signet-ring cell carcinoma, solid adenocarcinoma with mucin production, mucinous bronchioloalveolar carcinoma, mucinous ("colloid") adenocarcinomas and/or mucinous cystadenocarcinoma, and mucoepidermoid carcinoma, according to the World Health Organization classification [16]. Signet-ring cell carcinoma, solid adenocarcinoma with mucin production, and mucinous BAC are characterized by tumor cells containing abundant mucin in their cytoplasm. Signet-ring cell carcinoma and solid adenocarcinoma with mucin production form solid nests and exhibit an invasive growth pattern, whereas mucinous BAC is composed of tall columnar cells growing along alveolar walls without stromal invasion. Therefore, mucinous BAC might have a less invasive behavior and a better prognosis than signet-ring cell carcinoma and solid adenocarcinoma with mucin production [20].

In terms of immunohistochemical characteristics, signet-ring cell carcinoma and solid adenocarcinoma with mucin production showed a high expression of cytokeratin (CK) 7 (both 100%), and thyroid transcription factor-1 (TTF-1) (81.1% and 100%, respectively), but were both negative for CK20; mucinous BAC showed high expression of CK7 (94.7%), but low expression of CK20 (30.7%) and TTF-1 (27.5%) [20]. However, patients with goblet cell-type mucinous carcinoma are frequently immunoreactive for CK20, and the coordinated expression of TTF-1 and CK7 may also be present [15]. The immunohistochemistry of mucinous carcinoma of the lung is summarized in Table 1. The mucinous BAC of our patient was immunoreactive to TTF-1 and CK7, but negative for CK20. The immunohistochemical display manifested a typical pattern of lung adenocarcinoma, but could not be differentiated from other mucinous carcinoma of the lung. These markers appear to have limited value in the differential diagnosis of these mucinous lung cancers, and other immunohistochemical markers, such as CDX2, MUC2 and MUCAC5, are needed [15].

Primary lung carcinomas, particularly mucinous BAC, might be indistinguishable from carcinoma metastatic to the lung, such as colorectal cancer. Within the pulmonary adenocarcinoma group, nonmucinous bronchioloalveolar carcinoma and well differentiated adenocarcinoma have the highest prevalence of TTF-1 reactivity and are predominantly CK7+/CK20-. In contrast, colorectal cancer does not express TTF-1, and is predominantly CK7-/CK20+ [4, 7]. Nevertheless, mucinous BAC shows positive staining for TTF-1 of only 30% [7, 21-22]. It has been reported

Table 1. Comparison of immunohistochemical presentations of pulmonary mucinous carcinoma and mucinous adenocarcinoma of the colon

	TTF-1	CK7	CK20	CDX2	MUC2	MUC5AC
Goblet cell mucinous carcinoma of the lung	73-80%	82%	55%	100%	100%	18%
Signet-ring cell carcinoma of the lung	82-100%	82-100%	6-55%	0%	100%	18%
Mucinous bronchioloalveolar carcinoma of the lung	0-30%	83-100%	0-90%	0%	0%	100%
Mucinous carcinoma of the colon	0%	0%	100%	Positive	Positive	Variable

Reference from 3-15, 20-22, 25

also that 40% of mucinous bronchioloalveolar carcinoma cases showed CK7+/CK20-, and 60% of cases showed CK7+/CK20+ [12]. Therefore, it is difficult to distinguish mucinous bronchioloalveolar carcinoma from mucinous colorectal adenocarcinoma metastatic to the lung based only on the TTF-1, CK7 and CK20 phenotypes (Table 1). The expression of TTF-1 and the cytokeration profile in the tumor cells of our patient supported the pulmonary origin of the tumor. In addition, she did not have a history of gastrointestional malignancy, and the whole body bone scan and PET scan revealed no metastatic lesion. Therefore, the diagnosis of primary lung bronchioloalveolar carcinoma in our patient could be confirmed.

Bronchioloalveolar carcinoma showed good overall survival with appropriate surgical resection. The 5-year overall survival of BAC patients was 48% [23]. There are many preoperative prognostic factors for patients with BAC: chest radiography findings suggesting multiple lesions or lobar pneumonitis (large diffuse infiltrates), positive bronchoscopic washing or sputum cytology, and the presence of symptoms were associated with a poor prognosis [1]. Pathological features may also predict long-term survival. The presence of multiple tumors, diffuse malignant invasion, and mucin-producing tumors were associated with a worse prognosis [1]. Nonmucinous BACs are predominantly solitary lesions with a 5-year survival rate of 72%, whereas mucinous BAC has a more frequently diffuse pattern and a 5-year survival rate of 26% [24]. This patient had cough with productive sputum but no dyspnea or chest pain. Chest radiography and computed tomography revealed a lobar consolidation, but sputum cytology was negative. The histologic type was mucinous BAC. No evidence of recurrence or metastatic lesions was noted. However, due to the relatively poor prognosis, long-term close follow-up is necessary.

In summary, mucinous BAC constitutes a heterogeneous immunohistochemical profile and is associated with an impaired outcome. It is crucial to differentiate mucinous BAC from mucin-producing adenocarcinoma of the lung and adenocarcinoma metastatic to the lung by the clinical features, histopathology change and immunohistochemical analysis. Early aggressive pulmonary resection must be executed, and offers the potential for cure. Long-term follow up is also necessary.

References

1. Richard CD, Victor FT, Peter CP, *et al*. Bronchoalveolar carcinoma: factors affecting survival. Ann Thorac Surg 1991; 51: 368-77.
2. Raz DJ, He B, Rosell R, *et al*. Bronchioloalveolar carcinoma: a review. Clin Lung Cancer 2006; 7 :313-22.
3. Rubin BP, Skarin AT, Pisick E, *et al*. Use of cytokeratins 7 and 20 in determining the origin of metastatic carcinoma of unknown primary, with special emphasis on lung cancer. Eur J Cancer Prev 2001; 10: 77-82.
4. Tot T. Cytokeratins 20 and 7 as biomarkers: usefulness in discriminating primary from metastatic adenocarcinoma. Eur J Cancer 2002; 38: 758-63.
5. Kummar S, Fogarasi M, Canova A, *et al*. Cytokeratin 7 and 20 staining for the diagnosis of lung and colorectal adenocarcinoma. Br J Cancer 2002; 86: 1884-7.
6. Scarpatetti M, Tsybrovskyy O, Popper HH. Cytokeratin typing as an aid in the differential diagnosis of primary versus metastatic lung carcinomas, and comparison with normal lung. Virchows Arch 2002; 440: 70-6.
7. Chang YL, Lee YC, Liao WY, *et al*. The utility and limitation of thyroid transcription factor-1 protein in primary and metastatic pulmonary neoplasm. Lung Cancer 2004; 44: 149-57.
8. Johansson L. Histopathologic classification of lung cancer: Relevance of cytokeratin and TTF-1 immunophenotyping. Ann Diagn Pathol 2004; 8: 259-67.
9. Jerome MV, Mazieres J, Groussard O, *et al*. Expression of

TTF-1 and cytokeratins in primary and secondary epithelial lung tumours: correlation with histological type and grade. Histopathology 2004; 45: 125-34.

10. Moldvay J, Jackel M, Bogos K, *et al*. The role of TTF-1 in differentiating primary and metastatic lung adenocarcinomas. Pathol Oncol Res 2004; 10: 85-8.
11. Yatabe Y, Mitsudomi T, Takahashi T. TTF-1 expression in pulmonary adenocarcinomas. Am J Surg Pathol 2002; 26: 767-73.
12. Saad RS, Cho P, Silverman JF, *et al*. Usefulness of Cdx2 in separating mucinous bronchioloalveolar adenocarcinoma of the lung from metastatic mucinous colorectal adenocarcinoma. Am J Clin Pathol 2004; 122: 421-7.
13. Shah R, Badve S, Papreddy K, *et al*. Expression of cytokeratin 20 in mucinous bronchioloalveolar carcinoma. Mod Pathol 2000; 33: 915-20.
14. Lau SK, Desrochers MJ, Luthringer DJ. Expression of thyroid transcription factor-1, cytokeratin 7 and cytokeratin 20 in bronchioloalveolar carcinomas: an immunohistochemical evaluation of 67 cases. Mod Pathol 2002; 116: 319-25.
15. Murer B, Cavazza A , *et al*. Primary mucinous (so-called colloid) carcinomas of the lung: a clinicopathologic and immunohistochemical study with special reference to CDX-2 homeobox gene and MUC2 expression. Am J Surg Pathol 2004; 28: 442-52.
16. Travis WD, Brambilla E, Muller-Hermelink HK, *et al*. World Health Organisation Classification of Tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon, France: IARC Press; 2004: 10.
17. Chen KY, Chang CH, Yu CJ, *et al.* Distribution according to histologic type and outcome by gender and age group in Taiwanese patients with lung carcinoma. Cancer 2005; 103: 2566-75.
18. Travis WD, Lubin J, Ries L, *et al*. United States lung carcinoma incidence trends: declining for most histologic types among males, increasing among females. Cancer 1996; 77: 2464-70.
19. Travis W, Travis L, Devesa S. Lung cancer. Cancer 1995; 75: 191-202.
20. Tsuta K, Ishii G, Nitadori J, *et al*. Comparison of the immunophenotypes of signet-ring cell carcinoma, solid adenocarcinoma with mucin production, and mucinous bronchioloalveolar carcinoma of the lung characterized by the presence of cytoplasmic mucin. J Pathol 2006; 209: 78-87.
21. Saad RS, Liu YL, Han H, *et al*. Prognostic significance of thyroid transcription factor-1 expression in both early-stage conventional adenocarcinoma and bronchioloalveolar carcinoma of the lung. Hum Pathol 2004; 35: 3-7.
22. Goldstein NS, Thomas M. Mucinous and nonmucinous bronchioloalveolar adenocarcinomas have distinct staining patterns with thyroid transcription factor and cytokeratin 20 antibodies. Am J Clin Pathol 2001; 116: 319-25.
23. Pascal D, Bernard G, Clothilde R, *et al*. Bronchoalveolar carcinoma. Chest 1998; 113: 391-5.
24. Manning JT, Spjut HJ, Tschen JA. Bronchioloalveolar carcinoma; the significance of two histopathologic types. Cancer 1984; 54: 525-34.
25. Merchant SH, Amin MB, Tamboli P, *et al*. Primary signet-ring cell carcinoma of lung: immunohistochemical study and comparison with non-pulmonary signet-ring cell carcinomas. Am J Surg Pathol 2001; 25: 1515-9.

黏液型細支氣管肺泡癌—一病例報告與免疫組織化學染色的評估及預後之文獻回顧

陳崇裕　張逸良 *　陳冠宇　李元麒 **　楊泮池

黏液型細支氣管肺泡癌是肺腺癌中一種少見的組織型態。不同的臨床症狀、放射線表現與不同類型細支氣管肺泡癌的病理發現都和病人的存活率有密切的關係。黏液型細支氣管肺泡癌在組織型態上與其他肺部原發的黏液型腫瘤和轉移的黏液型腺癌極為相似。目前常用的免疫組織化學染色法中， Thyroid Transcription Factor (TTF-1)， Cytokeration (CK) 7 和 CK20 可以用來幫助區別原發性肺腺癌或轉移性腺癌。所以經由免疫組織化學的研究來對肺腺癌加以分類，可以幫助我們建立診斷及預後的推測。我們報告一個 68 歲的女性黏液型細支氣管肺泡癌患者，一開始是在胸部 X 片上右下肺葉的地方發現一個塊狀的陰影。她順利地接受了右下肺葉切除術與淋巴腺切除，在我們的門診追蹤至今並沒有發現腫瘤復發的情形。我們回顧了有關黏液型細支氣管肺泡癌免疫組織化學染色的研究與預後相關之文獻報告。*(胸腔醫學 **2007; 22: 98-105**)*

關鍵詞：細支氣管肺泡癌，免疫組織化學染色，甲狀腺轉錄因子 1 ，細胞角質蛋白

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Cough-Induced Rib Fracture in Osteopenic Patients

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Wann-Cherng Perng, Horng-Chin Yan

We report 3 patients with rib fractures induced by coughing. The diagnosis was confirmed by chest plain film showing the callus formation of rib fracture sites. The patients' body mass indexes were around the normal range. They all received a lumbar spine bone densitometry examination. The T scores were between -1.0 and -2.5 SD, indicating that these patients had osteopenia. Although cough-induced rib fractures can also occur in normal-bone-density patients, osteopenia or osteoporosis could be a risk factor of rib fractures. ***(Thorac Med 2007; 22: 106-110)***

Key words: cough, rib fracture, bone densitometry, osteopenia

Introduction

The causes of rib fractures can be classified into 3 categories: (i) traumatic; (ii) pathologic and (iii) stress [1]. Repetitive coughing paroxysms can induce rib stress fractures [2].

Chronic cough, like repeated submaximal musculoskeletal loading during athletic training, leads to rib remodeling [3]. The remodeling is attributed to osteoclast-mediated resorption and osteoblast-mediated repair [3]. When osteoclast activity prevails, rib stress fracture may occur. Based on this mechanism, chronic repetitive cough would induce rib fractures more often than acute forceful cough. This report presents 3 cases of patients with cough-induced rib fractures all of whom received a lumbar spine bone densitometry examination.

Case Reports

A 21-year-old Taiwanese male visited our clinic because of chronic dry cough. He had a common cold 3 months ago and chronic dry cough developed subsequently. He was given some symptom relief medication at a local medical clinic, but the dry cough continued to bother him. Two months prior to his visit, a sudden onset of severe left anterolateral chest pain developed after severe coughing. Soft tissue inflammation was diagnosed at a local clinic and he received a non-steroid anti-inflammation drug. Because of persistent chronic dry cough, he visited our clinic.

He had a half pack-per-day smoking habit for the last 2 years. His previous medical history was unremarkable. No chest local tenderness was

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found and the results of laboratory tests were within normal range. However, the chest plain film revealed multiple callus formation on the left 6th, 7th, and 8th (figure 1) and right 7th, and 8th ribs (figure 2).

An antitussive drug was prescribed and the chronic dry cough symptom improved gradually over 1 month. Three months after the first visit, the pulmonary function test revealed no obstructive ventilation impairment. However, the lumbar spine bone densitometry showed osteopenia.

Three patients presented with rib fractures in our clinic in a 3-months period (Table1). Their clinical histories were similar and no chest trauma history was noted. They simply caught a common cold and chronic cough developed subsequently.

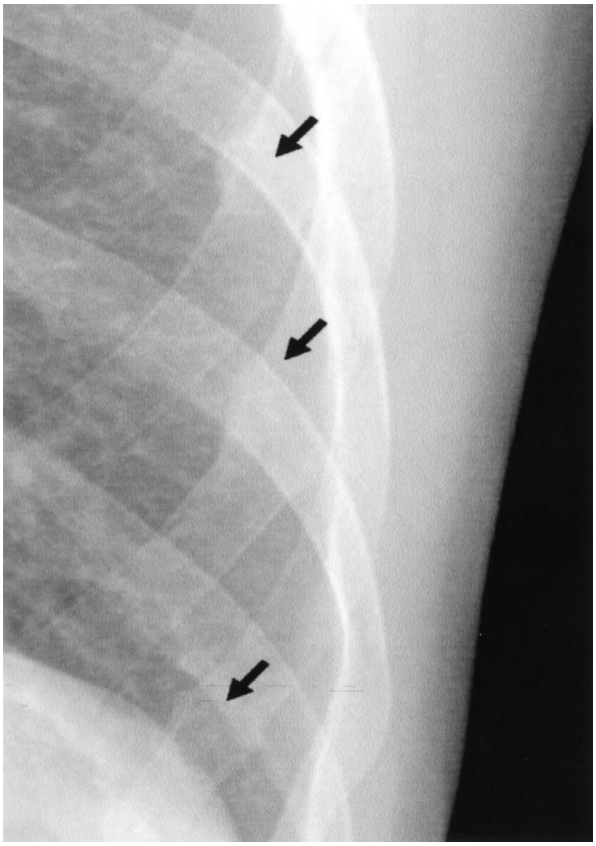

Fig. 1. Plain radiography showing callus formation (arrow) on the left 6th, 7th, and 8th ribs.

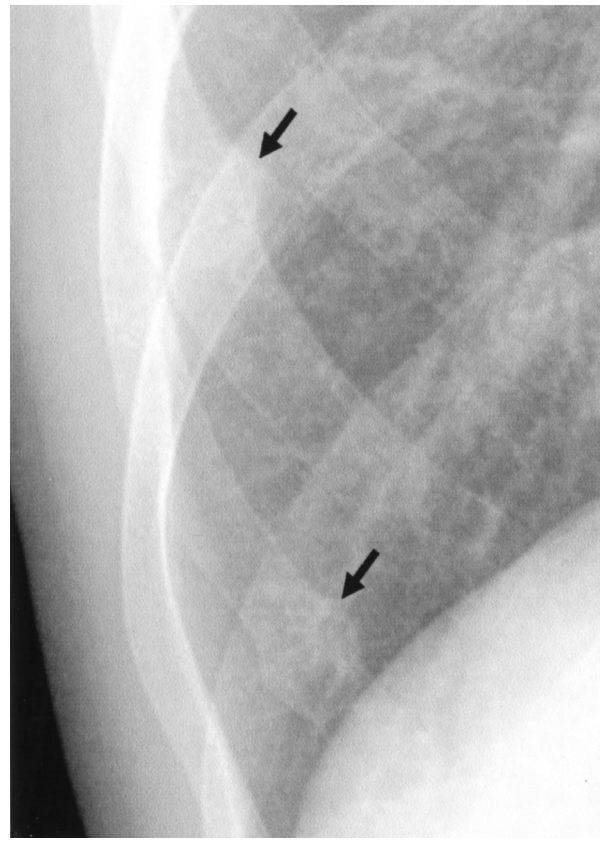

Fig. 2. Plain radiography showing callus formation (arrow) on the right 7th, and 8th ribs.

The duration between the onset of cough and the attack of acute severe chest pain was from 1 to 4 months. The numbers of rib fractures were 5, 1 and 2, individually. The diagnoses were proven by chest plain film showing callus formation 2 to 4 months after the acute chest pain. The patients' body mass indexes were around 18.3 to 24.6 kg/m^2. They all received a lumbar spine bone densitometry examination, and their T scores were between -1.0 and -2.5 SD. These results revealed that they were osteopenic.

Discussion

In these cases, repetitive cough followed by acute severe chest pain was initially found. The callus formation site shown on the chest radio-

Table 1. Three patients with rib fractures

Case	1	2	3
Age (years old)	21	45	39
Sex	male	female	male
Location of fractured ribs	Left 6th to 8th; Right 7th.8th	Left 6th	Right 4th.6th
Number of fractured ribs	5	1	2
From cough to chest pain (month)	1	4	1
Duration between onset of acute chest pain and the X-ray finding of abnormality (month)	2	2	4
BMI* (kg/m^2)	18.3	19.8	24.6
Bone densitometry T score (SD)**	-1.1	-2.1	-1.2

L: left side; R: right side

*BMI: body mass index

**SD: standard deviation; Normal: The value is above -1.0 SD; Osteopenia: The value is between -1.0 and -2.5 SD; Osteoporosis: The value is below -2.5 SD.

graph was the site of acute chest pain. The diagnosis of cough-induced rib fracture was made by the history and the chest plain film 2 to 4 months after the acute chest pain onset.

Since the non-displaced rib fracture is hard to find by chest plain film, the diagnosis of cough-induced rib fracture would often be delayed or underestimated. The diagnostic rate for rib fractures by chest plain film is only 60% [2]. If a detailed X-ray is taken, the diagnostic rate may rise to 92%. Clinically, if rib fracture cannot be ruled out, bone scan scintigraphy [4] or helical computer tomography [5] can be arranged to confirm the diagnosis.

According to the literature [6], cough-induced rib fractures mainly occur in the female. The average age is approximately 50 years. Most patients have had cough for more than 3 weeks, and 35% of the patients felt sudden chest pain after the coughing. Cough-induced rib fracture is easily induced at the 5th to 9th rib; half of patients had more than 1 rib fracture. However, reduced bone density is not a confirmed potential risk factor.

It is logical to assume that an unsound rib is more easily destroyed than a healthy rib. In our cases, the body mass indexes of the 3 patients were 19.8, 18.3 and 24.6 kg/m^2; they were near normal weight. When lumbar spine bone densitometry was performed, the results were all in the osteopenic range, but no obvious underlying disease was found when they received follow-up evaluation in our clinic. Although rib fractures can occur in normal bone density patients [6], osteopenia or osteoporosis could be a potential risk factor.

The treatment of the rib fracture is supportive. Antitussive drugs, analgesia, and anti-inflammation drugs could be prescribed for symptom relief. It is advised to reduce or stop intense activity for 4 to 6 weeks [7]. Surgical intervention is usually not necessary. The prevention of cough-induced rib fractures is through finding the underlying cause of the coughing and treating it. Before effective treatment is obtained, coughing softly is a good rib fracture preventive measure.

References

1. Prasad S, Baur LA. Fracture of the first rib as a consequence of pertussis infection. J Paediatr Child Health 2001; 37: 91-3.
2. Connolly LP, Connolly SA. Rib stress fracture. Clin Nucl Med 2004; 29(10): 614-6.
3. Lanyon LE. Functional strain as a determinant for bone remodeling. Calcif Tissue Int 1984; 35: 56-61.
4. Oren V, Kozenitzky I, Babiacki A, *et al.* Unusual cough related stress injuries. Eur J Nucl Med 1988; 14: 108-11.
5. De Maeseneer M, De Mey J, Debaere C, *et al.* Rib fractures induced by coughing: an unusual cause of acute chest pain. Am J Emerg Med 2000; 18: 194-7.
6. Hanak V, Hartman TE, Ryu JH. Cough-induced rib fractures. Mayo Clin Proc 2005; 80(7): 879-82.
7. Boden BP, Osbahr DC, Jimenez C. Low-risk stress fracture. Am J Sports Med 2001; 29: 100-111.

骨質缺乏病患之咳嗽引起肋骨骨折

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慢性咳嗽可以引起壓力性肋骨骨折。文中報導五名因咳嗽導致肋骨骨折之案例，其中一個案例為肋骨移位型骨折，另四位案例乃是藉由胸部 X 光片顯示假骨質形成(callus formation)來診斷。所有病人的身體質量指數都趨近正常值，其中三位病人接受骨質密度檢測，骨密度之 T 分數介於 -1.0 與 -2.5 標準偏差數，表示這三位病人都有骨質缺乏的狀況。雖然咳嗽引起肋骨骨折也可以發生在正常骨質的病人身上，但是骨質缺乏或者骨質疏鬆應為咳嗽導致肋骨骨折之危險因子。*(胸腔醫學* ***2007; 22: 106-110****)*

關鍵詞：咳嗽導致肋骨骨折，假骨質形成，骨質密度，骨質缺乏

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Carcinoid Tumor Arising in Mature Teratoma of the Anterior Mediastinum — A Case Report

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Apart from the gonads, the mediastinum is the most frequently involved site of germ cell tumors, accounting for about 2-6% of these neoplasms. Mature teratomas of the mediastinum are benign lesions. They do not have the metastatic potential observed in testicular teratoma, and are cured by surgical resection alone. Most teratomas of the mediastinum are benign and only 15-20% account for malignant neoplasms, such as immature teratomas, mature teratomas with malignant transformation, or teratomas concomitant to mixed germ cell tumors. Many lesions are found on routine chest X-rays, and nearly two-thirds of patients have specific symptoms. The most common symptoms are chest pain, cough, and dyspnea caused by compression or invasion of contiguous structures. Only 2 cases have been published in the past decades. We present a case of mature teratoma of the anterior mediastinum with carcinoid tumor arising in association with gastrointestinal epithelium, confined to the mass, and review the associated literature. ***(Thorac Med 2007; 22: 111-116)***

Key words: carcinoid tumor, mediastinal mass, teratoma

Introduction

Apart from the gonads, the mediastinum is the most frequently involved site of germ cell tumors, accounting for about 2-6% of these neoplasms [1-3]. Thymic lesions are most frequent in adults with primary anterior mediastinal tumors, and the vast majority is thymoma. Lymphoma is the second most common tumor, followed by endocrine and germ cell neoplasms (roughly equal in incidence). In children, lymphoma is the most common primary anterior mediastinal tumor. Germ cell neoplasms are the second most prevalent tumor, followed by thymic lesions and mesenchymal tumors. Germ cell tumors account for 1-15% of mediastinal neoplasms in adults, and 25% of mediastinal neoplasms in children [4-5]. Teratomas make up 80% of germ cell tumors in the mediastinum [2]. Benign teratomas are the most common mediastinal germ cell tumors. The majority of mediastinal teratomas are mature teratomas that are histologically well-defined and benign. If a teratoma contains fetal tissue or neuroendocrine tissue, it is defined as immature and malignant.

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Case Report

In this 40-year-old woman, a routine chest X-ray in the posterio-anterior view showed a tumor-like shadow in the right upper anterior mediastinum. The patient had had no complaints in association with this lesion; however, she was referred to the chest outpatient department at Chung-Ho Memorial Hospital, Kaohsiung Medical University, where further chest X-ray and chest computed tomography (CT) were arranged for her. Chest X-ray (Figure 1) showed a right upper anterior mediastinal tumor suspected to be a teratoma. In addition, chest CT (Figure 2) showed a 6 × 5 × 3.5 cm, well-circumscribed low attenuation mass with a fatty component at the right upper anterior mediastinum. She was admitted to the Chest Medicine Division of the Internal Medicine Department for further survey. The hematological, biochemical, coagulation, and spirometric examination results were within normal limits. Her complete ECG showed non-specific change, and she denied having symptoms or signs of ischemic heart disease. Elective operation was arranged under the impression of an anterior mediastinal mass suspected to be a teratoma.

This patient underwent a surgical operation on the 18th of March 2005. Intraoperative examination revealed a smooth bordered tumor, 8.3 × 5.1 × 4.7 cm in size, without infiltration of the surrounding organ, in the anterior mediastinum between the left innominate vein, the posterior part of the SVC, the pleura, and the pericardium.

The specimen submitted consisted of a mass, measuring 8.3 × 5.1 × 4.7 cm. Grossly, a grayish flesh mass, well-circumscribed with a smooth surface, was found. On cross section, a cyst with turbid yellow fluid, yellow friable debris, and hair was seen. Microscopically, cystic spaces lined by squamous epithelium and columnar to cuboid epithelium were observed. Mature skin append-

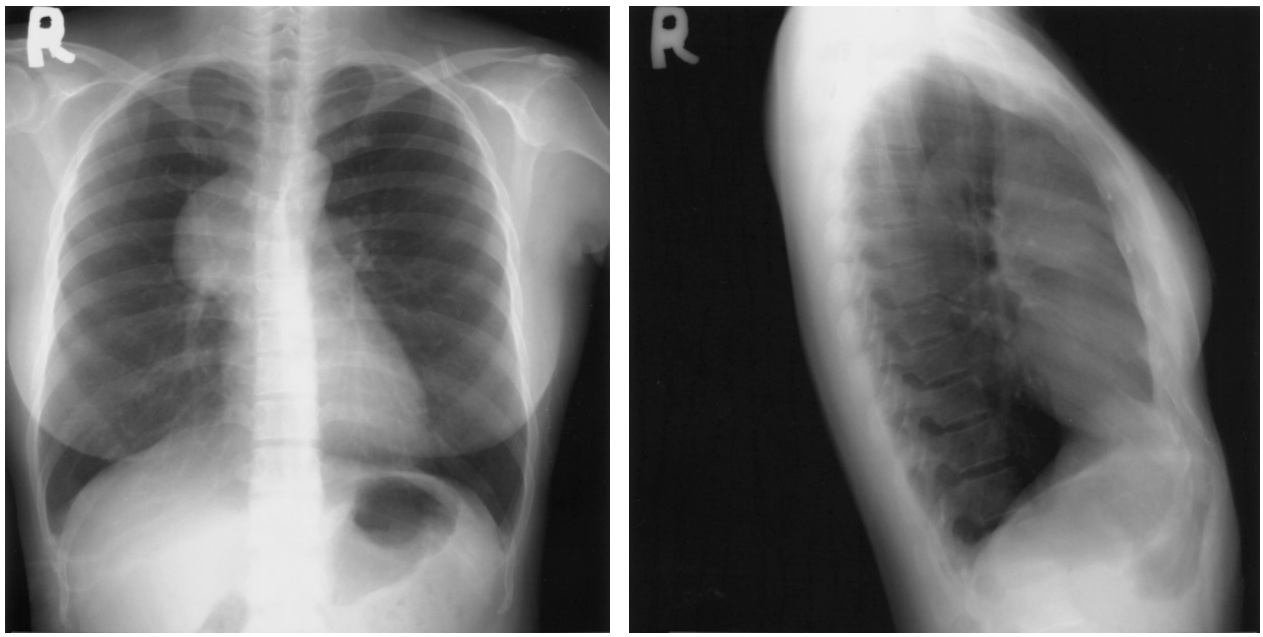

Fig. 1. Chest posteroanterior view shows a well defined right mediastinal mass; chest lateral view shows a right anterior mediastinal mass suspected of being a teratoma.

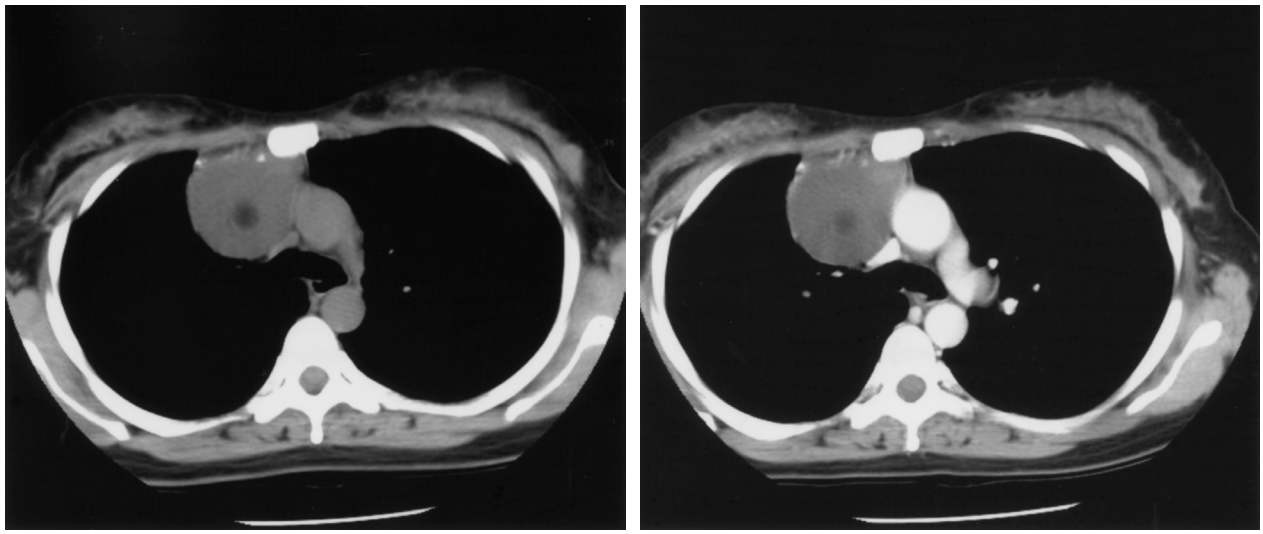

Fig. 2. Chest computed tomography with a mediastinal window without (left) and with contrast enhancement (right). A 6×5×3.5 cm, well circumscribed low attenuation mass with a fatty component at the right anterior upper mediastinum with adjacent superior vena cava is compressed and displaced. No enlarged mediastinal lymph nodes are noted.

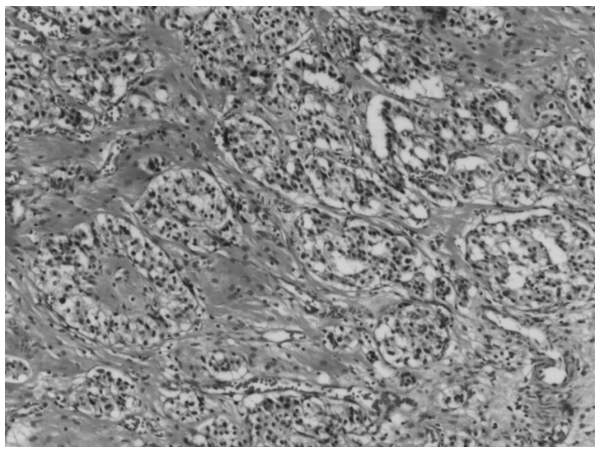

Fig. 3. Carcinoid tumor component is composed of small acini and solid nests of uniform polygonal cells with ample amounts of cytoplasm, and round or oval, centrally located hyperchromatic nuclei (original magnification X 400).

ages, salivary glands, mature cartilage, fibroadipose tissue, glial tissue, and smooth muscle cells were also seen. Carcinoid tumor, confined to the mass, and arising in association with the gastrointestinal epithelium present in the mature cystic teratoma was seen in 1 area (Figure 3). The tumor was composed of a collection of small acini and solid nests of uniform polygonal cells with ample amounts of cytoplasm, and round or oval, centrally located hyperchromatic nuclei. Immunohistochemical study showed cytokeratin(+), chromogranin A(+) and synaptophisin(+) (Figure 4) of the tumor cells.

The postoperative course was smooth; the general condition of the patient was good and wound healing was uncomplicated. Thus, the patient was discharged on 23 March 2005. She remained under observation at 6-month intervals. Chest X-ray revealed normal lungs and mediastinal shadow.

Discussion

Most germ cell tumors within the mediastinum localize in the anterosuperior segment, and only a few tumors have been diagnosed in the posterior mediastinum [6]. The mediastinum is the most frequently involved site of germ cell tumors, second only to the gonads, and accounts for about 2-6% of these neoplasms [1-3]. The

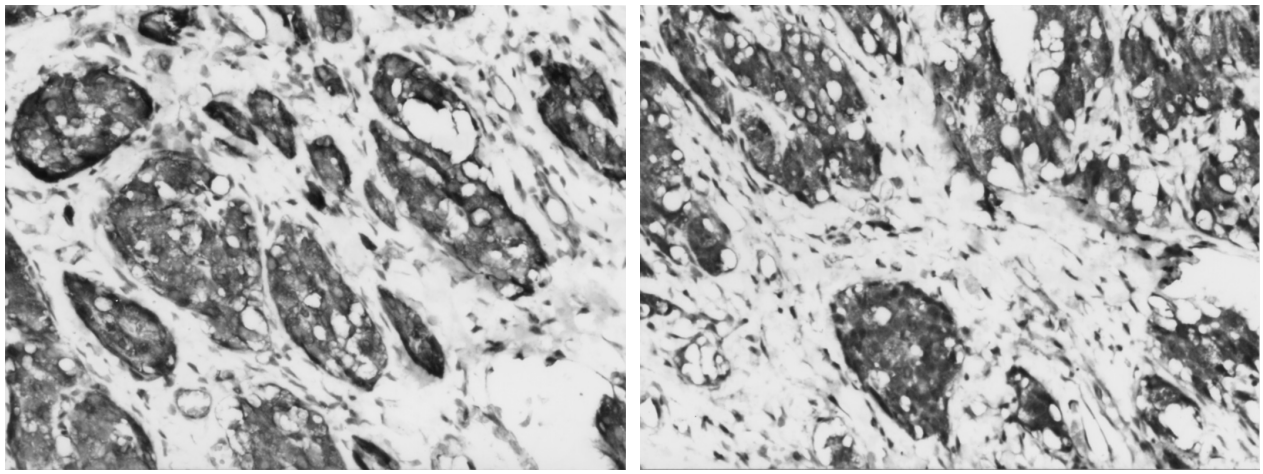

Fig. 4. The tumor cells are positive for chromogranin A and positive for synaptophysin immunostain (original magnification X 400).

histological structure of mediastinal germ cell tumors, including teratomas, is identical to that of tumors developing within the gonads [7]. Most teratomas of the mediastinum are benign and only 15-20% [5] account for malignant neoplasms, such as immature teratomas, mature teratomas with malignant transformation, or teratomas concomitant to mixed germ cell tumors. Teratomas in the mediastinum are more frequent in children and young adults. Germ cell tumors of the mediastinum are equally frequent in patients of either sex [3, 5]. Our patient was a 40-year-old woman who had a routine chest X-ray, in the posterior-anterior view, which showed a tumor-like shadow in the right upper anterior mediastinum.

A variety of signs and symptoms ranging from those clearly nonspecific to those virtually pathognomonic may cause the patient with an anterior mediastinal tumor to be seen for evaluation. Although many lesions are found on routine chest X-rays, nearly two-thirds of patients have specific symptoms [8]. The most common symptoms are chest pain, cough, and dyspnea caused by the compression or invasion of contiguous structures. Chest pain usually signals the invasive spread of malignant neoplasia. Other less common symptoms include hemoptysis, dysphagia, hoarseness, Horner's syndrome, vena caval obstruction, arrhythmias, fever, weakness, and weight loss [9]. The presence of symptoms in a patient with an anterior mediastinal mass clearly has prognostic importance because malignant lesions are more often symptomatic than benign lesions [8, 10]. In the normal group of symptomatic patients, approximately half of the lesions will be benign and half malignant [11]. Our case was asymptomatic at presentation, with the lesion being detected on routine chest X-ray examination.

Chest X-ray is most frequently used in the clinical diagnosis of germ cell tumors of the mediastinum, sometimes showing calcifications within the tumor. CT scans and magnetic nuclear imaging help in precisely localizing the tumor and in partly establishing its character [6]. The CT appearance of mediastinal teratoma is quite variable because it depends upon the content of the lesion. Almost all lesions have some areas of water attenuation on CT. Regions of fat attenuation are seen on CT in up to three-quarters of lesions, and are the predominant type. A definite cyst wall, which may have curvilinear calcification, may be visible on CT, as is characteristic

intralesional calcification. The CT findings of our case showed a well circumscribed low attenuation mass with a fatty component at the right anterior upper mediastinum.

A carcinoid may coexist along with other germ cell tumors, including containing structures arising from 2 or 3 germ layers. Carcinoid tumors have traditionally been classified according to their presumed derivation from different embryonic divisions of the gut [12].

Atypical and malignant carcinoids arising in the thymus without a germ cell tumor are considerably more frequent. Several case reports with carcinoid tumor in a mature teratoma of the kidneys, gonads, and spinal cord were noticed, but they were limited in the mediastinum. In a literature review, 2 cases of mature teratoma combined with goblet cell carcinoid on mediastinal germ cell tumors have been described in recent decades [2, 7]. Our case report is the 3rd case and is interesting because of the rarity of teratoma in association with a carcinoid.

Treatment of choice in cases of mature mediastinal teratoma is surgical excision of the tumor followed by histopathological examination to type the tumor and exclude immature tissue elements or the presence of other malignant epithelial or nonepithelial neoplasms which may develop within teratomas. Teratomas with malignant transformation or immature teratomas additionally require chemotherapy [13-14], carrying a poorer prognosis than mature teratomas. Due to the rarity of these cases, further standard treatment is not well established. More follow-up of these cases is necessary to assist in establishing proper treatment standards.

References

1. Aliotta PJ, Castillo J, Englander LS, *et al*. Primary mediastinal germ cell tumors: histologic patterns of treatment failures at autopsy. Cancer 1988; 62: 982-4.
2. Lancaster KJ, Liang ChY, Myers JC, *et al*. Goblet cell carcinoid arising in mature teratoma of the mediastinum. Am J Surg Pathol 1997; 21: 109-13.
3. Nichols CR. Mediastinal germ cell tumor. Cancer. Semin Thorac Cardiocasc Surg 1992; 4: 45-50.
4. Davis RD, Oldham HN, Sabiston CD. Primary cysts and neoplasms of mediastinum: recent changes in clinical presentation, methods of diagnosis, management and results. Ann Thorac Surg 1987; 44: 229-37.
5. Saabye J, Elbirk A, Anderson K. Teratomas of the mediastinum. Scand J Thorac Cardiovasc Surg 1987; 21: 272.
6. Lewis BD, Hurt RD, Payne WS, *et al*. Benign teratomas of mediastinum. J Thorac Cardiovasc Surg 1983; 86: 727-31.
7. Lucyna R, Bolestaw P, Eugeniusz M. Mature cystic teratoma of the mediastinum containing a carcinoid. A case report. Pol J Pathol 1998; 49(4): 309-12.
8. Silverman NA, Sabiston DC Jr. Primary tumors and cysts of the mediastinum. Curr Probl Cancer 1977; 2: 1.
9. Bradley M, J. David R. Primary anterior mediastinal tumors in children and adults. Ann Thorac Surg 1986; 42: 338-45.
10. King RM, Telander RL, Smithson WA, *et al*. Primary mediastinal tumors in children. J Pediatr Surg 1982; 17: 512.
11. Oldham HN Jr. Sabiston DC Jr. Primary tumors and cysts of the mediastinum. Monogr Surg Sci 1967; 4: 243.
12. Matthew H, Kulke, Robert J. Carcinoid tumors. N Engl J Med 1999; 340: 858-68.
13. Ulbright TM, Loehrer PJ, Roth LM, *et al*. The development of non-germ cell malignancies within germ cell tumors. Cancer 1984; 54: 1824-33.
14. Wirtanen GW, Stephenson JA, Wiley AL. Primary anterior mediastinal malignant teratoma. A case report with long-term survival. Cancer 1989; 63: 1823-5.

自前縱膈腔成熟畸胎瘤產生之類癌瘤—一個病例報告

李玫萱　陳煌麒　周世華 *　楊曉芳 **　黃明賢

除了性腺外，縱膈腔是生殖細胞瘤最好發的位置約佔百分之二至六。縱膈腔之成熟畸胎瘤大多是良性病變。縱膈腔之成熟畸胎瘤不像是睪丸畸胎瘤可觀察到的轉移潛力且可經由單獨外科切除治癒。大部分縱膈腔畸胎瘤是良性的，百分之十五至二十是惡性腫瘤，如不成熟畸胎瘤、成熟畸胎瘤併惡性轉形、畸胎瘤共存的混合生殖細胞瘤。在大部分的病變中是藉由常規胸部 X 光檢查發現，近三分之二的病患有特殊症狀。常見的症狀是因為鄰近構造被壓迫到或被侵犯到，如胸痛、咳嗽、呼吸急促。在英文文獻裡，過去的幾十年中只有兩個病例被發表過。在此我們提出一位自前縱膈腔之成熟畸胎瘤的胃腸道細胞產生之類癌瘤，並回顧歷年來與此病例相關的文獻報告。*(胸腔醫學 **2007; 22: 111-116**)*

關鍵詞：類癌瘤，縱膈腔腫塊，畸胎瘤

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Multicentric Castleman's Disease Presenting with a Mediastinal Mass, Multiple Lymphoadenopathy, Pleural and Pericardial Effusion — A Case Report and Literature Review

Shung-Ru Chen, Gwan-Han Shen, Guan-Chou*, Jeng-Yuan Hsu

Castleman's disease (CD, angiofollicular lymph node hyperplasia), is a lymphoproliferative disorder associated with a number of malignancies, including Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and POEMS syndrome. CD comprises at least 2 distinct diseases: i.e., localized and multicentric forms with very different prognoses. Herein, the case of a 52-year-old otherwise healthy female who suffered from chronic cough with whitish sputum, intermittent neck and face swelling, mediastinal mass, axillary lymphoadenopathy, and pleural and pericardial involvement for 3 months is reported. Multicentric Castleman's disease was diagnosed after axillary lymph node biopsy. Due to patient refusal, treatment with prednisolone 10 mg BID (bis in die) alone was given instead of chemotherapy; her symptoms, such as dyspnea, edema, facial swelling and fever, improved gradually. There was no recurrence after 1 and a half year's follow-up. ***(Thorac Med 2007; 22: 117-122)***

Key words: Castleman's disease, multicentric

Introduction

Castleman's disease (CD) was first described in 1954 and further defined in 1956 by Castleman as a lymphoproliferative disorder. It tends to present 2 different patterns of involvement: the first type is focal, localized or unicentric, whereas the second type includes diffuse multicentric disease with systemic manifestations. Localized CD is generally asymptomatic and usually discovered during a routine chest radiographic examination. The lesions may persist for many years without changing size. The masses are usually lobulated, generally not calcified, and mostly with smooth margins, and are found by computerized tomography (CT) scan to be very vascular. These solitary masses can be diagnosed as CD only by wide, often excisional biopsy; smaller specimens typically yield nonspecific results.

Multicentric CD frequently presents with systemic symptoms, including fever, night sweats, weight loss, fatigue and neuropathy, and tends to involve the peripheral lymph nodes, including the neck, retroperitoneum, pelvis and axillary

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nodes, rather than the lung or the mediastinum. Laboratory findings may include anemia, hypergammaglobulinemia and autoimmune phenomena [1].

In this report, we present a 52-year-old female who suffered from chronic cough with whitish sputum and intermittent neck and face swelling for 3 months. The initial chest image revealed widening of the mediastinum with bilateral pleural effusion, and pericardial effusion was noted the following day.

Case Report

A 52-year-old female was previously well and denied any past or family history of systemic disease. She came to our chest medicine outpatient clinic due to mild dyspnea and fever up to 38°C. She had suffered from productive cough with whitish sputum for 3 months. Intermittent face and neck swelling was noted on severe coughing. Daily night sweats, palpitation, poor appetite, general malaise and epistaxis were also mentioned for 10 days. Bilateral leg edema and decreased urine output with weight gain of 2 kilograms were noted in the most recent 2 months. Chest film revealed widening of the upper mediastinum and bilateral pleural effusion (Figure1). Under the impression of suspected lymphoma with superior vena cava syndrome or primary tuberculosis, she was admitted to our ward for further evaluation.

After admission, the hemogram showed anemia (hemoglobin 7.3g/dl), thrombocytopenia (50000/cumm), hyponatremia (120 mEq/L), hypoalbuminemia (2.6 g/dl), elevatedβ2-M (10410 ng/ml) (normal range 800-2400 μg/L), and serum creatinine (1.8 mg/dl). Chest CT showed pericardial effusion, bilateral pleural effusion, multiple mediastinal lymphoadenopathy and axillary lymphoadenopathy (Figures 2.1 & 2.2). Gallium scan revealed increased uptake in the right pulmonary hilum, bilateral lower lungs and nasal region. Fever was also noted during hospitalization. However, no definite fever source could be identified. Thoracentesis revealed an exudative effusion with lymphocytes predominant; however, bacterial culture, tuberculosis culture and cytology of the pleural effusion were all negative. The abdominal CT scan also yielded nega-

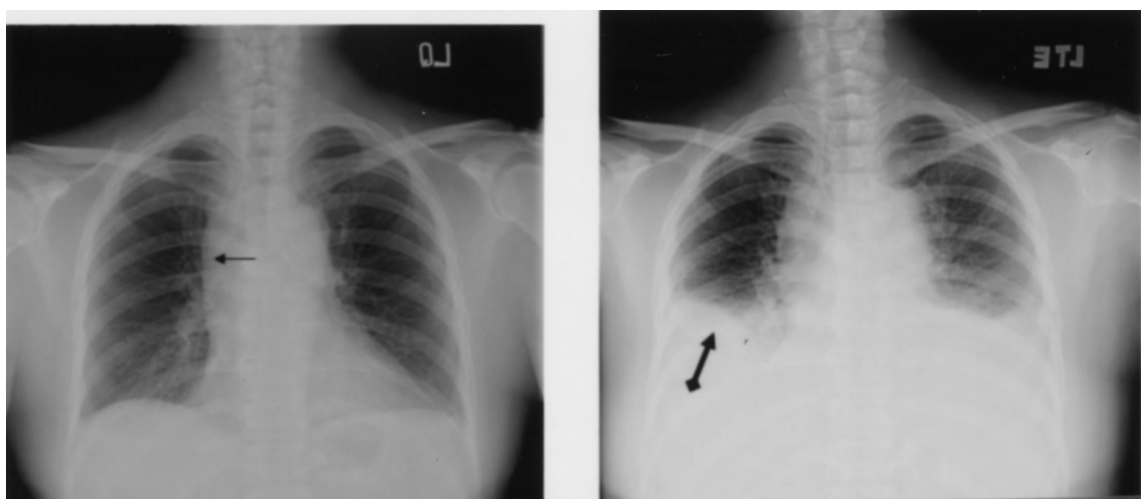

Fig. 1. Chest radiogram showing widening of the mediastinum (left) and increased pleural effusion and pericardial effusion 8 days later (right).

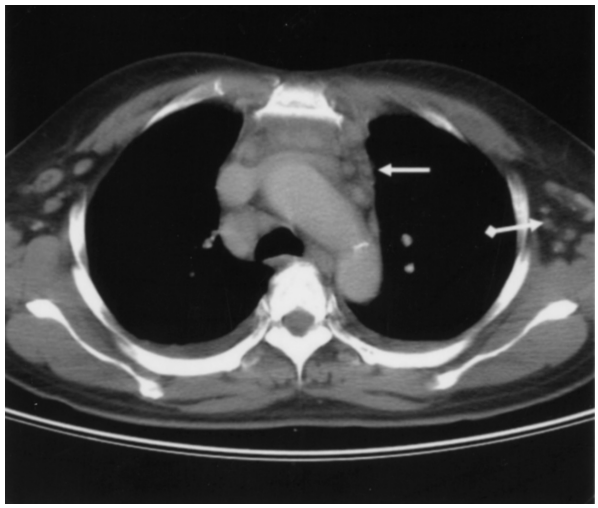

Fig. 2.1. Chest CT scan showing multiple lymphoadenopathy in the mediastinum (upper white arrow) and axilla (lower white arrow) 1 day after the first chest radiogram.

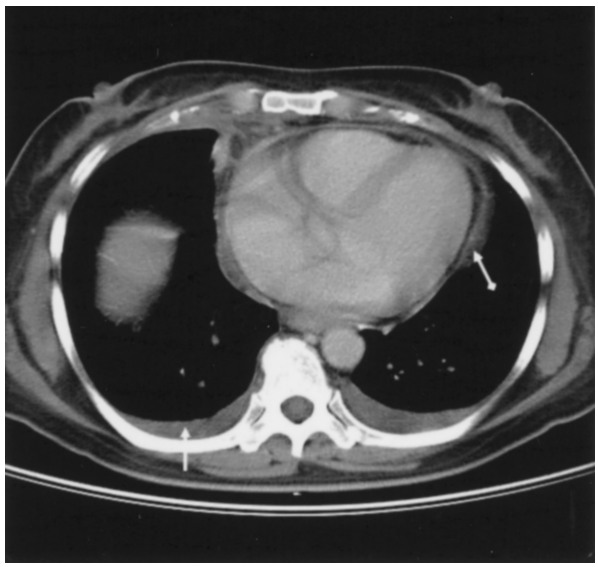

Fig. 2.2. Chest CT scan showing pericardial effusion (upper white arrow) and pleural effusion (lower white arrow) 1 day after the first chest radiogram.

tive results.

Mediastinoscopy with lymph node biopsy was negative for malignancy. Bone marrow biopsy showed hypocellular bone marrow only. To get the definite diagnosis, biopsy of the axilla lymph node was done again, and mixed-type

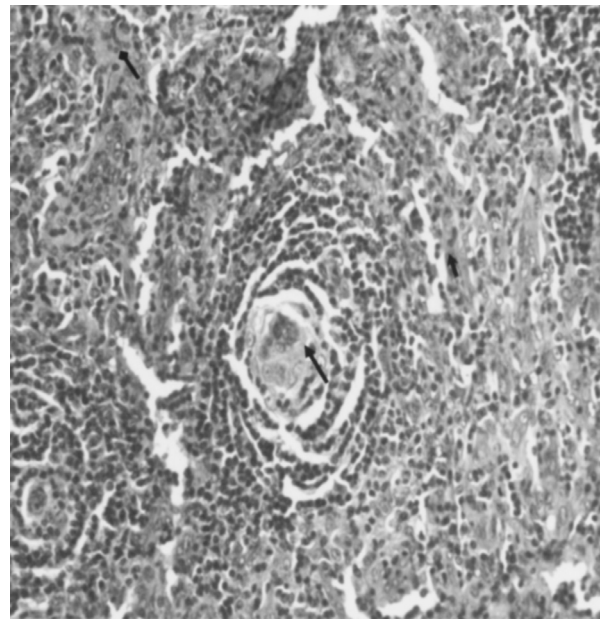

Fig. 3. Section of lymph node showing many small lymphoid follicles. Interfollicular marked hyperplasia of postcapillary venules and the presence of sheets and clusters of mature plasma cells with polyclonal light chains can be seen. Castleman's disease, multicentric, with features of both a hyaline vascular type (central black arrow) and plasma type (bilateral black arrow). [Hematoxylin and Eosin x200]

features of both hyaline vascular and plasma cell types were found. Multicentric Castleman's disease (MCD) was diagnosed (Figure 3). Pig-tail drainage was done for massive bilateral pleural effusion and dyspnea during hospitalization, with a poor yield. Oral prednisolone with 15 mg BID was tried. An elevated uric acid level (uric acid: 16.2 mg/dl) and deterioration of renal function (creatinine: 1.8 mg/dl) were noted 2 days later. Tumor lysis syndrome was considered [8], so the prednisolone was then held. After adequate hydration and medical treatment, the renal function improved gradually.

Steroid therapy with prednisolone 10 mg BID was prescribed again 2 weeks later. Symptoms including dyspnea, edema, face swelling and fever all improved gradually, and a normal uric acid level and serum creatinine were also noted.

Further chemotherapy was suggested, but the patient hesitated. Virus survey for HIV (human immunodeficiency virus) and herpes were negative. The patient was discharged with maintenance low-dose prednisolone. No recurrence was noted in 1 and a half year's follow-up.

Discussion

The heterogeneity of the pathologic classification of CD has been described as a hyaline vascular variant, plasma cell variant, and mixed variant [2]. The unicentric presentation is most common in the hyaline vascular variant. It responds well to surgical resection and is associated with a benign course [3]. Plasma or mixed variant types commonly present as multicentric involvement. This presentation requires systemic therapy and the prognosis is guarded. Associated systemic symptoms are common. There is an increased incidence of CD in patients with HIV [4], and the human herpes virus-8 is associated with nearly all of the HIV-associated CD cases and nearly 50% of non-HIV cases. Paraneoplastic and autoimmune entities are not uncommon in the disorder [5]. Interleukin (IL)-6 has also been shown to play a significant role in the pathogenesis of the disease [6]. In this patient, we could find paraneoplastic symptoms and tumor lysis after management, but they were not related to HIV.

Patients with MCD present at a median age of 52 to 65, although those who are HIV positive tend to be younger. Fifty to 65% are male. Symptoms are common but nonspecific, and are suggestive of an inflammatory illness. Patients present with fever, which is nearly universal, as well as night sweats, weight loss, and weakness or fatigue. Less than 10% have been asymptomatic.

Treatment of CD depends on the type of disease. The nodules of unicentric CD are usually resected surgically, with excellent long-term results. When these lymphoid nodules are located in areas difficult to resect, they may be treated with radiation therapy [7]. MCD has been treated with corticosteroid, cytotoxic drugs such as in immunosuppressive therapy, and radiation therapy. The results of these various therapies have not been systemically reported; but in general, the more symptomatic the patient, the poorer the response, and the shorter the survival. The mean survival has varied from 2.5 to 84 months in various studies. The optimal treatment remains unknown; however, the therapy response may be evaluated by the inflammation severity, decreased C-reactive protein level, increased hemoglobin and albumin, as well as improvement of lymphoadenopathy and hypergammaglobulinemia.

Our patient represents the first report of bilateral pleural effusion and pericardial effusion as initial manifestations. Pathology showed features of both a hyaline vascular type and a plasma cell type, until the axilla lymph node biopsy was done, after oral prednisolone therapy. Tumor lysis syndrome was found, which may have been due to the large tumor burden, and the symptoms improved after tapering the dosage.

It is important to consider CD in the differential diagnosis for patients presenting with extensive lymphoadenopathy, no matter whether the patient is immunocompromised or not. The clinical index of suspicion for CD is heightened by the presence of fever of unknown origin and night sweats, HIV infection/AIDS, hypoalbuminemia, POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*ultiple myeloma, and *s*kin changes) syndrome, and hypergammaglobulinemia.

References

1. Akimoto Y, Ishiyama T, Kawakami K, *et al*. A patient with multicentric Castleman's disease with lymphoid interstitial pneumonia died of an aggressive course with adult respiratory distress syndrome. Rinsho Ketsueki 1995; 36: 742-8.
2. Aoki Y, Tosato G. Targeted inhibition of angiogenic factors in AIDS-related disorders. Curr Drug Targets Infect Disord 2003; 3: 115-28.
3. Azoulay E, Herry I, Antoine M, *et al*. Multicentric Castleman's disease with mediastinal involvement in a patient with HIV infection. Rev Mal Respir 1997; 14: 481-3.
4. Bollen JM, Polstra AM, Van Der Kuyl AC, *et al*. Multicentric Castleman's disease and Kaposi's sarcoma in a cyclosporin-treated, HIV-1 negative patient: case report. BMC Blood Disord 2003; 3: 3.
5. Day JR, Bew D, Ali M, *et al*. Castleman's disease associated with myasthenia gravis. Ann Thorac Surg 2003; 75: 1648-50.
6. Brousset P, Cesarman E, Meggetto F, *et al*. Colocalization of the viral interleukin-6 with latent nuclear antigen-1 of human herpes virus-8 in endothelial spindle cells of Kaposi's sarcoma and lymphoid cells of multicentric Castleman's disease. Hum Pathol 2001; 32: 95-100.
7. Bowne WB, Lewis JJ, Filippa DA, *et al*. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. Cancer 1999; 85: 706-17.
8. Duzova A, Cetin M, Gumruk F, *et al*. Acute tumour lysis syndrome following a single-dose corticosteroid in children with acute lymphoblastic leukaemia. Eur J Haematol 2001; 66:404-407.

以瀰漫性淋巴病變爲表現的多發性 Castleman 氏病 —一病例報告及文獻回顧

陳相如　沈光漢　周　冠 *　許正園

Castleman 氏病（血管濾泡淋巴結增殖），是一種淋巴增生性的疾病，因為它與人類免疫不全及第八型?疹病毒的密切關係而廣受注意，Castleman 氏病包括至少兩型疾病且有不同的預後，它與一些腫瘤有關，包括卡波西氏肉瘤、霍金氏及非霍金氏淋巴瘤和 POEMS 症候群。我們報告一位診斷為多發性 Castleman 氏病的 52 歲中年婦女，她以前的身體狀況良好，因咳嗽白痰及陣發性臉部及頸部腫脹三個月求診，因病患拒絕全身性化學治療，僅以口服類固醇控制，出院後門診追蹤一年半未見復發。*(胸腔醫學* ***2007; 22: 117-122)***

關鍵詞：Castleman 氏病，多發性

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Mother-Infant Transmission of *Mycobacterium Tuberculosis* Beijing Genotype Detected by Spoligotyping — A Case Report

Yu-Ming Hung, Ruwen Jou*, Hai-Chyi Peng**, Chia-Hsiang Chu***, Jen-Jyh Lee****, Yung-Hsiang Hsu*****

Spacer oligonucleotide typing (Spoligotyping), one of the molecular genotyping techniques, has been proven useful for simultaneous detection and genotyping of the *Mycobacterium tuberculosis* complex, and can be used in the epidemiological study of *Mycobacteria tuberculosis* infection. We report a 90-day-old infant, who suffered from fever and obstructive ileus treated with surgery. The pathological finding was intestinal tuberculosis. The infant's mother was found to have sputum smear and culture-positive pulmonary tuberculosis. Spoligotyping could be done from the pathological biopsy of the intestinal specimen. We found the same spoligotype of *M. tuberculosis*, the Beijing genotype, in the mother's sputum isolate and the infant's biopsy sample. Based on the contact history and the identical Beijing genotype, we highly suspected that the infant's intestinal tuberculosis was transmitted from his mother. ***(Thorac Med 2007; 22: 123-128)***

Key words: spoligotyping, epidemiological study of *Mycobacterium tuberculosis* infection, intestinal tuberculosis

Introduction

The standard genotyping method for *M. tuberculosis* isolates is restriction-fragment-length polymorphism (RFLP) analysis of the distribution of the insertion sequence IS6110 in different strains [1-3]. However, it is burdened by many drawbacks such as the need of mycobacterial cultural growth. Spoligotyping is one of the genotyping methods used in the identification and analysis of epidemiologic links within tubercular outbreaks. It allows the simultaneous detection and typing of the *M. tuberculosis* complex and is more discriminative in the analysis of strains with a low IS6110 copy number [2-3]. It can be applied directly to biological samples, biotic material,

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paraffin-embedded tissues, and Ziehl-Nielsen smears, and needs only a small amount of cultured DNA. The addition of DNA fingerprinting to conventional contact tracing as a tool to understanding the transmission of tuberculosis is valuable. We report herein a rare case of an infant with intestinal TB highly suspected to have been transmitted from his mother, who had active pulmonary TB, and used spoligotyping to determine the genotype.

Case Report

A gravida 4 para 2 mother delivered a 90-day-old, 2180-gm male infant by cesarean section at 38 weeks gestation. Breast feeding was started at birth. At 71 days old, the infant developed fever and rhinorrhea, lasting for 10 days. His mother brought him to hospital A, where he was admitted for antibiotics treatment. However, fever persisted and abdominal distension was noted. The stool was greenish and watery, and stool and blood cultures were negative for bacteria. After 9 days of treatment, the infant still showed no response, so he was transferred to Tzu-Chi General Hospital.

Physical examination revealed an infant with a globular, distended abdomen who was failing to thrive. Upon palpation of the abdomen, the infant showed muscle guarding and began crying. Greenish and watery stool was projected out during digital examination. The abdominal KUB showed distended bowel loops, but colon double contrast showed a smooth passage of the contrast and rather normal peristalsis, caliber, and haustration. The white blood cell count was 16,100/mm^3 with 11% band forms, 20.5% lymphocytes and 13.5% monocytes. The platelet count was 525,000/mm^3. Antibiotics with ampicillin plus cefametazole and metronidazole were given, and laparoscopy was performed 4 days later. Laparoscopic findings showed pus coating with adhesion along the peritoneal wall to the terminal ileum; there was also straw colored ascites in the right iliac fossa and yellowish granulomas studded on the mesentery and intestinal wall. The procedure was then converted to open laparotomy, and severe stricture of the terminal ileum about 20 cm proximal to the ileocecal valve was noted. The proximal intestinal loop was severely dilated. Segmental resection of the terminal ileum with a double-barrel enterostomy was performed. Histopathology of the resected terminal ileum showed granulomatous inflammation with caseous necrosis and numerous TB bacilli identified by acid-fast stain (Figures 1 and 2, respectively). He was diagnosed with intestinal tuberculosis and peritonitis. Anti-TB drugs (INH, Rifampicin, PZA) were started. The Mantoux skin test was negative, and the cerebrospinal fluid was normal. Sputum exam for AFB stains and TB culture were negative.

Contact investigation of the infant's family was done, and only his mother had tuberculosis. Her chest X-ray revealed infiltrations in the bilateral upper lobes and cavitations in the right upper

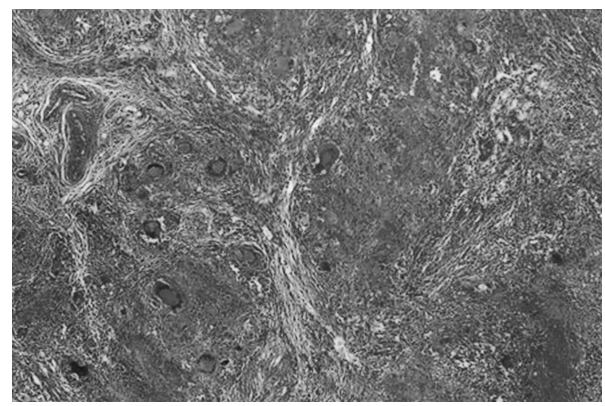

Fig. 1. Histopathology revealed granulomatous inflammation with Langerhans' giant cells and caseous necrosis diagnostic of tuberculosis in the ileum.

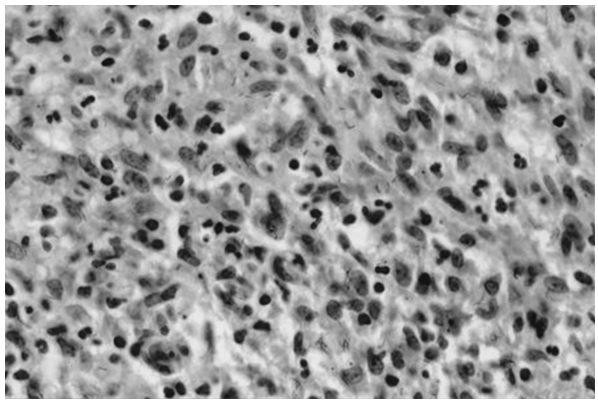

Fig. 2. Acid-fast stain of the infant's terminal ileum biopsy shows numerous TB bacilli, diagnostic of tuberculosis.

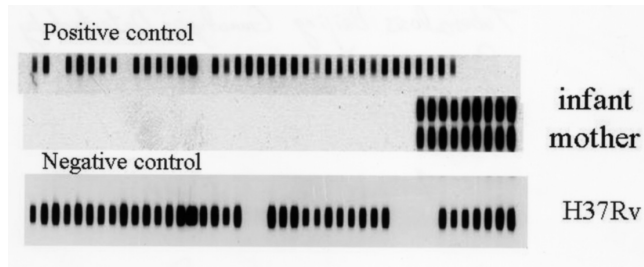

Fig. 3. Spoligotyping comparing both samples from the mother and the infant, with the last 9 spacers belonging to the Beijing family strain and the negative control of *M. bovis* reference strain H37Rv.

lobe. Sputum for TB culture and AFB were positive. Spoligotyping was used to detect the presence of M. tuberculosis complex DNA in the paraffin wax-embedded small bowel biopsy sample, and to help in the understanding of the transmission between the mother and infant. Spoligotyping of the isolates from the mother and the ileum biopsy sample of the infant showed identical Beijing genotypes, as shown in Figure 3.

Discussion

Extra-pulmonary TB is estimated to occur in 16% of patients not infected with human immunodeficiency virus (HIV), whereas the frequency is about two-thirds (including one-third with both pulmonary and extrapulmonary involvement) in patients infected with HIV [1].

Abdominal tuberculosis is a rare disease, and is defined as an infection of the peritoneum and hollow or solid abdominal organs by *Mycobacterium tuberculosis*. The peritoneum and the ileocecal region are the most likely sites of infection and are involved in the majority of cases by hematogenous spread or through swallowing of infected sputum from primary pulmonary tuberculosis. Pulmonary tuberculosis is apparent in less than one-third of patients. Abdominal tuberculosis has a frequency related to the severity of pulmonary involvement in 1%, 4.5% and 25% of patients with minimal, moderately advanced, and far advanced pulmonary tuberculosis, respectively [1, 4].

Congenital tuberculosis has been reported rarely. The diagnostic criteria for distinguishing congenital from postnatal acquired tuberculosis were established by Beitzke in 1935, but were revised and proposed by Cantwell *et al*. [5] in 1944. The modified criteria include proven tubercular lesions in the infant plus 1 of the following: (1) lesions occurring in the first week of life, (2) a primary hepatic TB complex or caseating hepatic granulomas, (3) tuberculous infection of the placenta or the maternal genital tract; or (4) exclusion of postnatal transmission by a contact investigation. In the present case, transmission linkage from the mother to the infant was highly suspected by spoligotyping of the *M. tuberculosis* isolates. The mother had TB during pregnancy and contact investigation found no alternative sources of infection. The infant came to medical attention at 80 days, not in the first 1-3 weeks. During the cesarean operation, hepatic granulomata were not found. The mother was not examined for uterine TB and the placenta was di-

scarded after the infant was born. The Mantoux test is frequently negative in newborns, and can take 1 to 3 months to become positive [6]. The mother began breastfeeding without difficulty; transmission via breastfeeding was unlikely, because the mother did not have TB mastitis [7]. Transmission could occur through hematogenous spread or swallowing of infected sputum from primary pulmonary tuberculosis, as described previously. Due to close contact with the infant, postnatal transmission was very likely. However, we do not have evidence to support the infant acquiring congenital tuberculosis during pregnancy.

In recent years, a large number of DNA fingerprinting methods have been available to type mycobacterial isolates. The standardized and most widely applied molecular method for *M. tuberculosis* isolates is IS6110 restriction fragment length polymorphism (RFLP) typing [2]. However, the effectiveness of IS6110 RFLP is limited when the *M. tuberculosis* isolates contain no, or less than 5 copies of IS6110 [2-3, 8]. Other disadvantages of RFLP typing are that it is technically demanding and expensive, and it requires sophisticated computer software to analyze the RFLP pattern and large DNA from culture of clinical material, which is time consuming; about 20-40 days are required before sufficient mycobacteria are available to obtain enough DNA for this method. This time restriction limits the usefulness of RFLP typing, especially in studying the possible nosocomial transmission of tuberculosis in a clinical setting.

Spoligotyping is a new method for the simultaneous detection and typing of *M. tuberculosis* complex bacteria. This method is based on polymerase chain reaction (PCR) amplification of a highly polymorphic direct repeat locus in the *M. tuberculosis* genome, and can be use to differentiate strains with fewer than 5 copies of IS6110 [2]. As in the present case, we can obtain bacterial DNA from non-viable material or paraffin-embedded material [2, 9-11], and have the results in less than 1 day using spoligotyping. Thus, the clinical usefulness of spoligotyping is highlighted by its rapidity, both in detecting causative bacteria and in providing epidemiologic information on strain identities. Implementing such a method in clinical settings would be useful in the surveillance of tuberculosis transmission and in interventions to prevent the further spread of this disease. Nonetheless, the discriminatory power of spoligotyping is less than that of IS6110 RFLP typing; spoligotyping could conceivably be used as an initial screening step before applying a secondary technique of greater discriminatory power [12-13]. The discriminatory power of spoligotyping makes it possible to classify *M. tuberculosis* strains into subspecies, such as the Beijing genotype. Although the IS6110 RFLP pattern of the Beijing strains is not unique and is often difficult to distinguish from other genotypes, the spoligotype is highly distinctive and easy to identify [13]. The Beijing genotype strains were highly prevalent in the Beijing area (more then 86% of the *M. tuberculosis* isolated from Beijing, China) [14], and have been reported to cause outbreaks throughout the world. Some strains of the Beijing family have been demonstrated to have high virulence, causing infection in BCG-vaccinated individuals, and more commonly causing infections in young people in Vietnam [15]; they are also related to the transmission of drug-resistant strains [16]. In a study conducted by Jou *et al*. in 2004 to investigate the distribution of the Beijing family genotypes in Taiwan [17], a large proportion of tuberculosis patients were found to be infected with Beijing family genotypes in the northern (51.6%) and eastern (46.2%) regions, as compared to the central (31.6%) and southern (28.0%) regions of

Taiwan. The prevalence of Beijing family genotypes in Taiwan was 44.4%.

Intestinal tuberculosis in the infant is a rare disease that is difficult to diagnose. A high index of suspicion is needed. For every tuberculosis case in an infant, contact investigation of the family is very important. Spoligotyping can be used to help understanding the transmission of tuberculosis. Conventional contact investigation should be coordinated with a molecular epidemiologic study to detect and treat possible cases of tuberculosis.

References

1. Hopewell PC, Bloon BR. Tuberculosis and other mycobacterial disease. In: Murray JF, Nadel JA, Mason RJ, *et al*. Textbook of Respiratory Medicine. 3rd edition. Philadelphia: W.B. Sanders Company 2000; 1043-105.
2. Van Soolingen D. Molecular epidemiology of tuberculosis and other mycobacterial infections: main methodologies and achievements. J of Inter Med 2001; 249: 1-26.
3. Barnes, PF, Cave MD. Molecular epidemiology of tuberculosis. N Engl J Med 2003; 349: 1149-56.
4. Gorbach SL. Tuberculosis of the gastrointestinal tract. Gastrointestinal Disease Pathophysiology, Diagnosis, Management. Philadelphia: WB Saunders Company, 1993; 2: 1158-61.
5. Cantwell MF, Shehab ZM, Costello AM, *et al*. Brief report: congenital tuberculosis. N Engl J Med 1994; 330: 1051-4.
6. Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax 2001; 56: 494-9.
7. Lawrence RM, Lawrence RA Breast milk and infection. Clin Perinatol 2004; 31: 501-28.
8. Woods GL. The mycobacteriology laboratory and new diagnostic techniques. Infect Dis Cli of North Am 2002; 16: 127-44.
9. Greer CE, BS, Peterson SL, *et al.* PCR amplification from paraffin-embedded tissues. Effects of fixative and fixation time. Am J Clin Pathol 1991; 95: 117-24.
10. van der Zanden AG, Hoentjen AH, Heilmann FG, *et al*. Simultaneous detection and strain differentiation of *Mycobacterium tuberculosis* complex in paraffin wax-embedded tissues and in stained microscopic preparations. Mol Pathol 1998; 51: 209-14.
11. Shibata D. Extraction of DNA from paraffin-embedded tissue for analysis by polymerase chain reaction: new tricks from an old friend. Hum Pathol 1994; 25: 561-3.
12. Goyal M, Saunders NA, Van Embden JD, *et al*. Differentiation of *Mycobacterium tuberculosis* isolates by spoligotyping and IS6110 restriction fragment length polymorphism. J Clin Microbiol 1997; 35: 647-51.
13. Burgos MV, Pym AS. Molecular epidemiology of tuberculosis. Eur Respir J 2002; 20: 54-65.
14. Van Soolingen D, Qian L, de Haas PE, *et al*. Predominance of a single genotype of *Mycobacterium tuberculosis* in countries of East Asia. J Clin Microbiol 1995; 33: 3234-8.
15. Anh DD, Borgdorff MW, Van LN, *et al*. *Mycobacterium tuberculosis* Beijing genotype emerging in Vietnam. Emerg Infect Dis 2000; 6: 302-5.
16. Friedman CR, Stoeckle MY, Kreiswirth BN, *et al*. Transmission of multidrug-resistant tuberculosis in a large urban setting. Am J Respir Crit Care Med 1995; 152: 355-9.
17. Jou RW, Chiang CY, Huang WL. Distribution of the Beijing family genotypes of *Mycobacterium tuberculosis* in Taiwan. J Clin Microbiol 2005; 43: 95-100.

母親與嬰兒間之北京株結核菌感染—病例報告

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間隔寡核酸基因分型法 (spoligotyping) 可以同時鑑定結核菌株及其基因型別，以應用於結核病分子流行病學的研究。本報告為一位九十天大的嬰兒因發燒和腸阻塞而開刀，病理報告為腸結核，追至嬰兒的母親也有肺結核。藉由間隔寡核酸基因分型法，在腸結核的病理切片組織中，我們找到與母親陽性痰液培養中相同的北京株結核菌。因此，高度懷疑嬰兒的結核病是由母親傳染而來。傳統的接觸史追蹤應佐以分子流行病學研究來確認及治療結核病。*(胸腔醫學* ***2007; 22: 123-128)***

關鍵詞：間隔寡核酸基因分型法，肺結核病分子流行病學，腸結核

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Clear Cell Variant Squamous Cell Carcinoma of the Lung — A Case Report

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Clear cell change in primary lung cancer is not uncommon, but clear cell-predominant bronchogenic carcinoma is extremely rare. The unique pathologic character of clear cells is large polygonal tumor cells with “water-clear” or foamy cytoplasm. Most of the reports had a favorable prognosis. A 72-year-old male was seen with persistent dry cough; chest radiography revealed a left upper lobe mass. After a detailed survey, left upper lobe lobectomy and lymph node dissection were performed. Clear cell changes were found on nearly all pathologic sections and only few tiny squamoid differentiations were found. Clear cell variant of squamous cell carcinoma was the final diagnosis. The patient had an early local recurrence and chest wall metastasis after 6 months which was a quite unusual clinical course. The presentation of majority clear cells of lung cancer required a complete review of all pathologic sections to find any squamous or glandular differentiation. Benign sugar tumors and metastasis from urinary tract malignancy should also be differentiated both by immunohistochemical stains and detailed radiographic survey. ***(Thorac Med 2007; 22: 129-134)***

Key words: clear cell variant of lung cancer

Introduction

Clear cell foci are a specific pathologic differentiation in bronchogenic carcinomas. Morgan and Mackenzie [1] reported 13 cases of clear cell carcinoma in 1964, in which the “water-clear” cells were microscopically polygonal cells containing clear cytoplasm. Clear cell changes could be found in 30% of lung carcinomas [2] but only 50 cases of clear cell carcinoma have been reported to date [3-7]. There is still debate about whether clear cell carcinoma constitutes a distinct clinicopathologic entity or represents clear cell variants of squamous or adenocarcinoma, since most reported cases show either squamous or glandular differentiation [8]. Herein, we present a case of predominantly clear-cell-containing bronchogenic carcinoma, which was finally diagnosed as a clear cell variant of squamous cell carcinoma. The subsequent clinical course is also included in this report.

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Case Report

A 72-year-old male came to our clinics for persistent dry cough for 2 months. Chest roentgenogram revealed a roughly 4-cm mass in the left upper lung. He denied other co-mobidities, but had a body weight loss of 2 kg in 2 months. He had a history of smoking of 1 pack per day for 60 years. Chest computed tomography (CT) showed a non-enhanced encapsulated cyst-like tumor in the left upper lobe without enlarged mediastinal lymph nodes (Figure 1). The abdominal sonography and bone scan were both negative for possible metastasis. The lung function test for assessment of pulmonary function revealed acceptable forced expiratory volume in 1 second. Left upper lobe lobectomy was carried out, and all mediastinal lymph node and surrounding fat was removed for complete staging. The specimen included a $4 \times 3 \times 2.5$-cm tumor with viscera pleural invasion. Microscopically, the mass showed nests of polygonal cells, which had clear cytoplasm, vesicular round to oval nuclei and inconspicuous nucleoli (Figure 2). Immunohistochemical study of these clear cells demonstrated positivity for cytokeratin, vimentin, cytokeratin 5/6 and epithelial membrane antigen (EMA), and negativity for smooth muscle actin (SMA), melanoma antibody (HMB-45), thyroid transcription factor-1 (TTF-1), and carcinoembryonic antibody (CEA). The bronchial margin, bronchial stump and all resected lymph nodes were all negative for malignancy. A preliminary diagnosis of clear cell carcinoma was given by the pathologist initially.

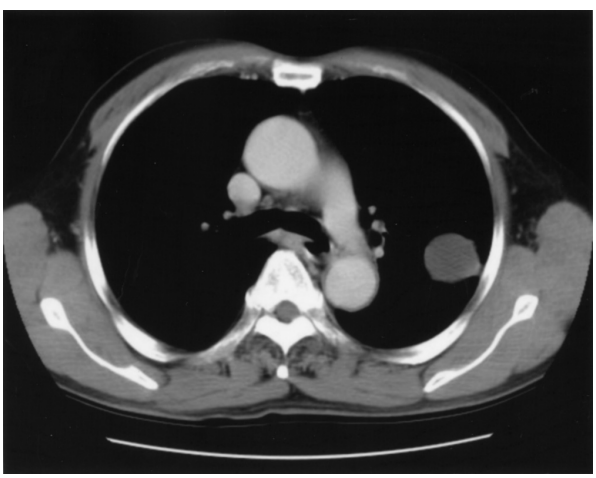

Fig. 1. Chest CT shows a non-enhanced encapsulated cyst-like tumor in the left upper lobe without enlarged mediastinal lymph nodes.

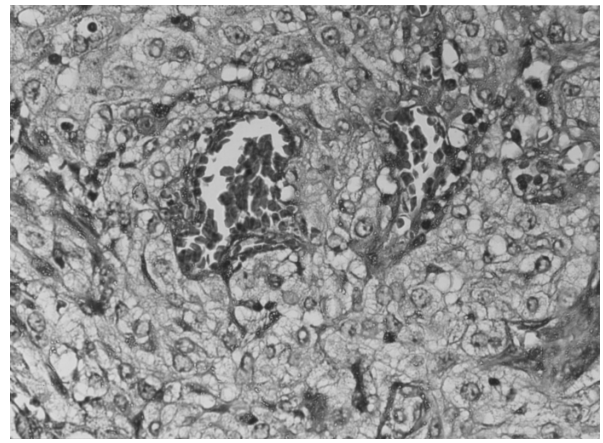

Fig. 2. The "water-clear" cells microscopically: polygonal cells containing clear cytoplasm, vesicular round to oval nuclei and inconspicuous nucleoli.

Soon after his recovery, a detailed urologic survey was arranged to determine a possible primary origin from the kidney, which was the most frequent site of clear cell carcinoma. But we could not find any evidence of renal tumor. After another exhaustive review of all pathologic sections, tiny squamoid differentiation was found in some sections (Figure 3). The pathologist concluded that this was a rare case of a clear cell variant of squamous carcinoma of the lung with pathological staging Ib (T2N0M0). The patient received adjuvant chemotherapy with cisplatin and paclitaxel 1 month after operation but quit after the first course because of intolerance.

Six months later, he suffered from frequent cough with some blood-tinged sputum, and

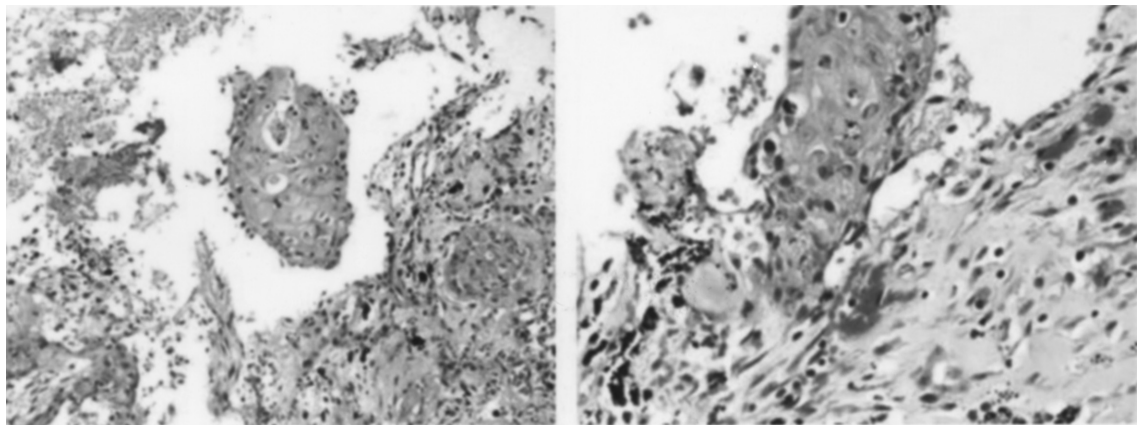

Fig. 3. Squamoid differentiation in 2 pathologic sections

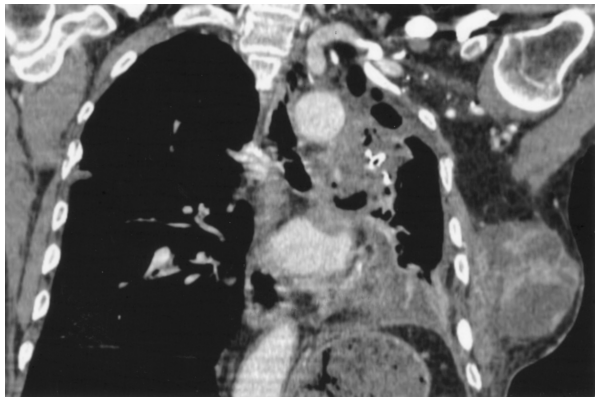

Fig. 4. Chest CT revealing a soft tissue nodule (3.6 × 4.1cm) in the left suprahilar region, and tumor metastasis of the left chest wall.

hemoptysis less than 10 ml on several occasions. A gradually enlarging palpable mass in the left chest wall was also mentioned. The chest CT revealed a metastatic left chest wall tumor (8.0 × 7.0 × 3.5 cm), and tumor recurrence (3.6 × 4.1 cm) in the left suprahilar region (Figure 4). We excised the left chest wall mass for pathological examination. Microscopically, it showed proliferative fibrous tissues intermingled with large-polygonal cells with clear or foamy cytoplasm simulating foamy histiocytes. The initial pathological impression was inflammatory pseudotumor. But immunohistochemical study of these specimens again demonstrated positivity for cytokeratin and vimentin. Therefore we concluded that this was a metastatic lesion from the pulmonary lesion.

The patient did not receive further adjuvant therapy because of a poor Eastern Cooperative Oncology Group (ECOG) performance status. In his admission (7 months after the first lung operation), he suffered from peritonitis due to perforated colon diverticulitis and received an emergecy laparotomy. He died from post-operative adult respiratory distress syndrome 7 days later though the abdominal condition remained satisfactory. No malignant cell was found in the pathology of the resected colon diverticulitis.

Discussion

In 1964, clear cell carcinoma of the lung was reported with features of mucin-rich tumor cells stained by diastase-resistant periodic acid Schiff reaction. The subsequent reports of clear cell carcinoma were solid tumors with large pools of glycogen without a mucinous component [3-7]. In 1980, a study [2] reported 105 (30%) clear cell changes in 348 consecutive resected lung cancers. Fifteen cases had more than 50% clear cell foci, 10 showed squamous foci and 4 showed adeno-

carcinomatous foci. Only 1 case (0.3%) had pure clear cells. A similar finding that there are variants in both ultrastructures and differentiation in clear cell-predominant tumors was also noted in another study [7] in 1985. This means that the previously reported and nominated clear cell carcinoma may not be a distinct clinicopathologic entity, and the classification of clear cell-predominant tumor is still in dispute. The World Health Organization, in 1999, defined clear cell carcinoma as large cell carcinoma with pure clear cell features. When squamous or glandular differentiation was seen with clear cell components, it was classified as clear cell variants of squamous cell carcinoma or adenocarcinoma [9]. In our case, clear cells constituted the majority of the tumor, and the differential diagnosis encompassed clear cell carcinoma of the lung, clear cell variant of adenocarcinoma or squamous cell carcinoma, metastatic tumors and clear cell sugar tumor.

For lung tumor mainly composed of "water-clear" or foamy cytoplasm, benign clear cell tumor, also known as sugar tumor, should be considered, this tumor has a histological appearance similar to clear cell carcinoma but with a different histogenesis and behavior [9]. The benign clear cell tumor grows less invasively and without metastatic intention, except in 1 report of hepatic metastasis which occurred 10 years after surgical resection [10]. Histologically, nuclear polymorphism is minimal and mitotic figures are hard to find. The sugar tumor expresses no epithelial marker including cytokeratin and epithelial membrane antigen and positive immunoreactivity of melanoma antibody (HMB-45), and S-100 protein [11-12]. In our case, the positive expression with cytokeratin and negative with HMB-45 excluded the possibility of benign clear cell tumor.

Clear cell carcinoma is the predominant cell type in renal cell carcinoma, at 75-85% [13], and has a histological appearance similar to pulmonary-originated ones. The diagnosis should only be made after excluding any possible urinary system tumors. In our case, we had a detailed survey of his urologic systems, by an experienced urologist, without any evidence of malignancy confirmed by abdominal CT. Other possible origins of clear cell tumor including the breast, hypopharynx, liver, and pancreas [14-17], were all carefully surveyed with negative findings. The final diagnosis of a clear cell variant of squamous cell carcinoma of the lung was made because of a few tiny squamoid differentiations were found on some sections.

The clinical presentation of pulmonary clear cell carcinoma in the literature was usually a peripheral mass [3], ranging from 3 cm to 8 cm in 1 series [7]. Almost all reports had a favorable prognosis although there are too few to be reliable. One investigator considers they are no better than the other non-small cell lung cancers. The tumor had a rapidly progressing course in our case. Although there were no mediastinal lymph node and distant metastasis, and the surgical bronchial margin was free of malignancy, bronchial stump and mediastinal lymph node recurrence were found 6 months after excision. We believe that the possibility of inadequate surgical excision is low and the rapidly progressive course was probably due to the nature of the cell type. The presence of the chest wall metastatic tumor was evidence of easy dissemination. This elicits suspicion of whether the squamoid component was an indicator of a worse outcome or just a prognosis similar to primary squamous cell carcinoma.

In conclusion, predominant clear-cell containing tumors of the lung are challengeing both in their histopathologic aspects and their clinical

managements. Careful histopathologic examination of the specimen for squamous or adenocarcinomatous differentiation should be done if clear cell components of lung cancer are seen. Immunohistochemical stains can serve as a differential diagnostic tool, especially for differentiating benign clear cell tumors. Any possible primary origin, especially the kidney, should undergo a detailed survey. The clinical course may be suboptimal. Even in the early stage, rapid progression and a dismal prognosis may occur.

References

1. Morgan AD, Mackenzie DH. Clear-cell carcinoma of the lung. J Pathol Bacteriol 1964; 87: 25-7.
2. Katzenstein AL, Prioleau PG, Askin FB. The histologic spectrum and significance of clear-cell change in lung carcinoma. Cancer 1980; 45(5): 943-7.
3. Coppola G, Bancale A, Oliva G. "Clear cell" carcinoma of the lung. Morphology, histochemistry, histogenesis, Ann Ist Carlo Forlanini 1965; 25(3): 280-97.
4. McNamee CJ, Simpson RH, Pagliero KM, *et al*. Primary clear-cell carcinoma of the lung. Respir Med 1993; 87(6): 471-3.
5. Yamamato T, Yazawa T, Ogata T, *et al*. Clear cell carcinoma of the lung: a case report and review of the literature. Lung Cancer 1993; 10(1-2): 101-6.
6. Garzon JC, Lai FM, Mok TS, *et al*. Clear cell carcinoma of the lung revisited. J Thorac Cardiovasc Surg 2005; 130(4): 1198-9.
7. Edwards C, Carlile A. Clear cell carcinoma of the lung. J Clin Pathol 1985; 38(8):880-5.
8. Gaffey MJ, Mills SE, Ritter JH. Clear cell tumors of the lower respiratory tract. Semin Diagn Pathol 1997; 14(4): 222-32.
9. World Health Organization. Histological Typing of Lung and Pleural Tumors, 3rd ed. Springer Verlag, Germany, 1999; 45-50.
10. Sale GE, Kulander BG. "Benign" clear-cell tumor (sugar tumor) of the lung with hepatic metastases ten years after resection of pulmonary primary tumor. Arch Path Lab Med 1988; 112: 1177-8.
11. Gaffey MJ, Mills SE, Zarbo RJ, *et al*. Clear cell tumor of the lung. Am J Surg Pathol 1991; 15: 644-53.
12. Gal AA, Koss MN, Hochholzer L, *et al*. An immunohistochemical study of benign clear cell ("sugar") tumor of the lung. Arch Pathol Lab Med 1991; 115(10): 1034-8.
13. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005; 353(23): 2477-90.
14. Pak I, Kutun S, Celik A, *et al*. Glycogen-rich "clear cell" carcinoma of the breast. Breast J 2005; 11(4): 288.
15. Trupiano JK, Ogrodowczyk E, Bergman S. Pathologic quiz case: mass in the right breast. Glycogen-rich clear cell carcinoma of the breast. Arch Pathol Lab Med 2003; 127 (12): 1629-30.
16. Nunez Rodriguez MH, Torres Nieto MA, Velicia Llames R, *et al*. Clear cell hepatocarcinoma Gastroenterol Hepatol 2003; 26(9): 615-7.
17. Batoroev YK, Nguyen GK. Clear-cell carcinoma of the pancreas in fine-needle aspirate. Diagn Cytopathol 2005; 32(4): 249-51.

透明細胞型鱗狀上皮細胞癌—病例報告

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在肺癌中透明細胞 (clear cell) 的分化並不少但幾乎由透明細胞所構成的肺癌相當罕見，透明細胞在顯微鏡下的病理表現為水樣透明的細胞質。由透明細胞構成的肺部腫瘤需要鑑別診斷的包括良性透明細胞瘤、原發或次發透明細胞癌、以及透明細胞型鱗狀上皮細胞癌或腺癌作鑑別診斷，因為預後截然不同。仔細的病理切片檢查，免疫化學染色和詳盡的泌尿系統檢查都是必須的。但在此我們提出一個屬於第一期的透明細胞型鱗狀上皮細胞癌病例，臨床症狀只有咳嗽，胸部 X 光片為左上肺葉一週邊腫瘤，而電腦斷層攝影下其密度為似囊狀病變，並無縱隔腔淋巴結腫大或遠處轉移。經根除性左上肺葉切除術後其病程進展及局部轉移相當快速。在此並回顧歷年來與此病例相關的文獻報告。*(胸腔醫學 **2007; 22: 129-134**)*

關鍵詞：透明細胞型鱗狀上皮細胞癌

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Huge Gastrointestinal Stromal Tumor Extending into the Left Thorax — A Case Report

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Gastrointestinal stromal tumors, a group of mesenchymal tumors with special immunohistochemical properties, usually arise from the gastrointestinal tract, but may occur in the omentum, mesentery, and retroperitoneum. They relatively rarely occur in young women.

We report a huge gastrointestinal stromal tumor in a young woman. The tumor was 16 x 10 x 10 cm in size and extended from the abdominal cavity to the left thorax. After chemotherapy with Glevic for 3 months, the tumor had enlarged (23 x 18 x 16 cm) with the mediastinum shifting to the right thorax. The patient received conservative treatment and expired due to multiple organ failure. ***(Thorac Med 2007; 22: 135-139)***

Key words: gastrointestinal stromal tumor

Introduction

Gastrointestinal stromal tumors (GISTs) are relatively rare tumors of the gastrointestinal tract. They are a group of mesenchymal tumors with specific immunohistochemical properties, and account for 1-3% of all gastrointestinal neoplasms [1]. They primarily develop in the gastrointestinal tract, but may also occur as primary tumors outside the gastrointestinal tract, such as in the omentum, mesentery, and retroperitoneum [2-5]. We describe a young female patient with a huge GIST extending into the thorax, with the left lung compressed and the mediastinum shifting to the right thorax. There have been no reports of such a huge GIST or a GIST extending into the thorax.

Case Report

This patient was a 26-year-old healthy female. She had complained of cough with whitish sputum, dyspnea, orthopnea and mild left chest pain for 2 weeks. Breathing sounds were decreased in the left thorax. The chest radiography showed pleural effusion in the left upper lung field, as well as a soft tissue mass near the left hilum and left lower lung field, with the mediastinum deviated to the right side (Figure 1). Chest computed tomography (CT) showed a huge lobulated radiolucent mass, measuring $16 \times 10 \times 10$ cm in size, with central necrosis. The mass occupied the left upper abdomen abutting the lesser curvature of the stomach and extended into the lower thorax. Left lower lobe lung compression

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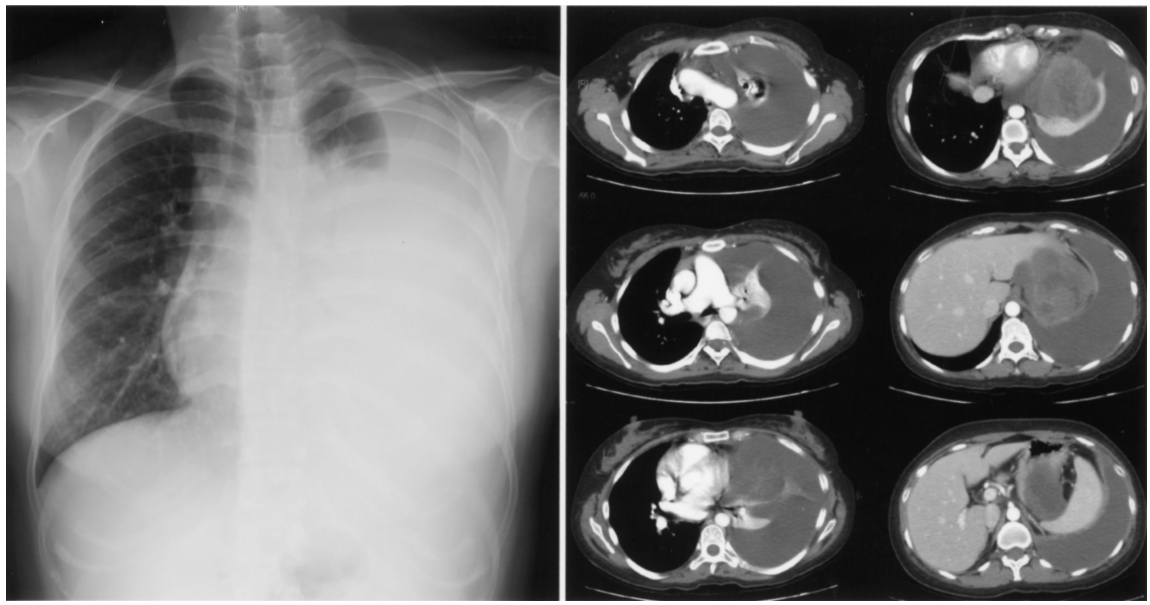

Fig. 1. Chest radiography and computerized tomography show a huge lobulated radiolucent mass in the left thoracic cavity with pleural effusion. The mediastinum was compressed to the right thorax. The mass measured 16 × 10 × 10 cm in size; central necrosis occupied the left upper abdomen abutting the lesser curvature of the stomach and extended across the left diaphragm and into the left lower thorax.

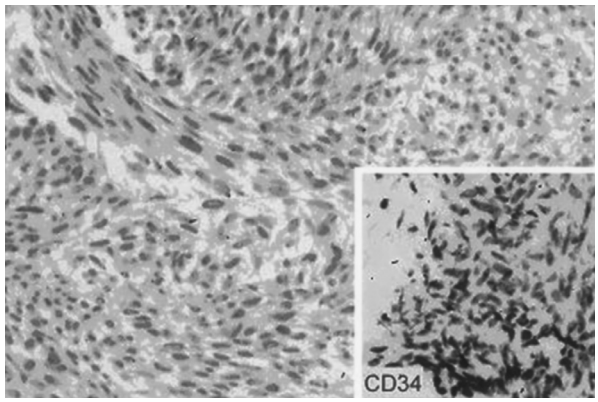

Fig. 2. The hematoxylin and eosin stain section (left side) showed a combination of spindle and epithelioid cell types. The CD34 stain section (right side) revealed partial positive, compatible with gastrointestinal stromal tumor.

due to the tumor and massive pleural effusion were noted. The pathology report of the CT guided biopsy showed spindle cell type, CD117(-), CD 34(+) (Figure 2) and S100 (focally weak positive), compatible with GIST. There were no malignant cells in the pleural effusion. Due to the huge size, and diaphragm and contiguous vital organ invasion, chemotherapy with Glivec was suggested. She followed up at our outpatient department. However, she complained of persistent dyspnea and bilateral lower limb pitting edema. The CT examination after 3 months' chemotherapy showed an enlarged tumor, 23 × 18 × 16 cm in size, with the mediastinum shifting to the right thorax (Figure 3). Multiple enlarged paratracheal and celiac lymph nodes were also noted, and metastasis was suspected. The patient was transferred to the intensive care unit and expired because of multiple organ failure.

Discussion

GISTs have 3 microscopic morphologies: spindle cell type (70%), epithelioid cell type (20%), or a combination of these 2 morphologies. GISTs are positive for the expression of the KIT receptor tyrosine kinase (CD117 antigen) in 95%

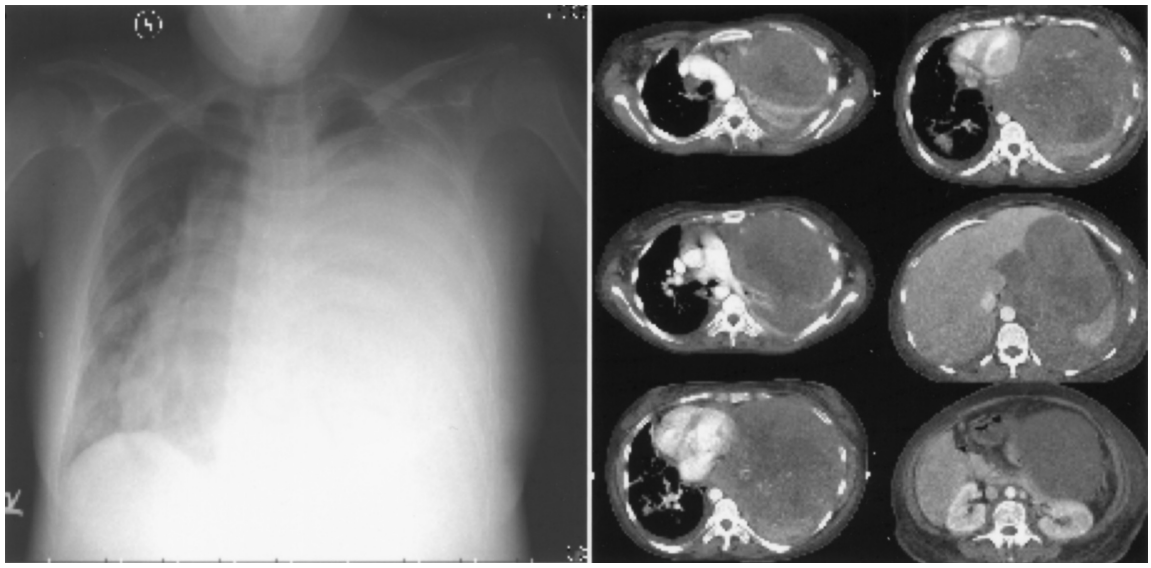

Fig. 3. Three months later, the tumor was enlarged with the mediastinum shifting to the right side, 23 × 18 × 16 cm in size. Multiple enlarged paratracheal and celiac lymph nodes were also noted, and metastasis was suspected on chest radiography and computerized tomography.

of cases. About 60-70% of GISTs stain for CD 34, 30-40% reacts to anti-smooth muscle actin (SMA), and approximately 5% is immunopositive for S-100 protein [6]. The CT scan guided biopsy with immunohistological stain in this case was negative for expression of CD117 and positive for CD 34 and S100, compatible with GIST.

GISTs generally occur after the age of 40, with a median age varying from 55 to 65 years, and are slightly more common in men [7]. About 5% of patients are under the age of 40 [8]. The incidence of patients under the age of 29 is 0.06 per 100,000 people [9]. This patient was a 26-year-old female, which is relatively rare according to previous studies.

The tumor was huge, 23 × 18 × 16 cm, and extended across the diaphragm into the thorax. There has been no report regarding such a huge GIST and no report of a GIST extending from the abdomen into the thorax. This GIST resulted in left lung compression and the mediastinum shifting to the right side. The patient presented with cough with whitish sputum, dyspnea, and orthopnea. There was no obvious gastrointestinal symptom.

We had no evidence regarding where the tumor had arisen from, but the tumor margin was clear, except in the lesser curvature of the stomach in the first CT scan, so this was the most likely origin of the tumor. The patient did not receive a panendoscopic examination or upper gastrointestinal series study due to her poor condition and dyspnea.

According to her family, she had no history of diaphragmatic disease. The left diaphragm, except the central area due to the tumor, could be tracked. Massive pleural effusion, but no ascites was noted. Diaphragmatic hernia or defect could be ruled out by the first CT scan.

The only curative therapy for GIST is complete surgical excision with negative histologic margins. When GISTs adhere to contiguous organs, consideration should be given to an en bloc resection [10]. Due to the huge size, and invasion

to the diaphragm and contiguous vital organs, we suggested chemotherapy with Glivec. However, there was no response to Glivec treatment. The tumor, as well as the paratracheal and celiac lymph nodes, were enlarged on the CT scan. Early en bloc resection may be of help when chemotherapy fails. However, the left pleural effusion in this case contributed to the inability to distinguish the real size of the tumor on the chest radiography. A repeat chest CT scan may have helped to confirm the real size of the tumor and make an early en bloc resection possible.

References

1. Sandrasegaran K, Rajesh A, *et al*. Gastrointestinal stromal tumors: CT and MRI findings. Eur Radiol 2005; 15: 1407-14.
2. Miettinen M, Monihan JM, *et al*. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol 1999; 23: 1109-18.
3. Sakurai S, Hishima T, *et al*. Gastrointestinal stromal tumors and KIT-positive mesenchymal cells in the omentum. Pathol Int 2001; 51: 524-31.
4. Reith JD, Goldblum JR, *et al*. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol 2000; 13: 577-85.
5. Fukuda H, Suwa T, *et al*. Gastrointestinal stromal tumor of the lesser omentum: report of a case. Surg Today 2001; 31: 715-8.
6. Miettinen M, El-Rifai W, *et al*. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. Hum Pathol 2002; 33: 478-83.
7. DeMatteo RP, Lewis JJ, *et al*. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231: 51-8.
8. Miettinen M, Lasota J. Gastrointestinal stromal tumors—definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001; 438: 1-12.
9. Tran T, Davila JA, *et al*. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005; 100: 162-8.
10. van der Zwan SM, DeMatteo RP. Gastrointestinal stromal tumor: 5 years later. Cancer 2005; 104: 1781-8.

延伸至左胸腔的巨大腸胃道基質瘤—個案報告

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腸胃道基質瘤 (gastrointestinal stromal tumor) 是一類具有特殊免疫組織化學性質的間質瘤，通常由腸胃道長出，但有時亦可由網膜、腸系膜或後腹腔長出。此種腫瘤少發生於年輕女性。

此篇病例報告是關於一發生於年輕女性之巨大腸胃道基質瘤。該腫瘤約在確定診斷時約 16 × 10 × 10 公分，且由腹腔一直延伸至左胸腔。經過以 Glevic 化學治療三個月後，該腫瘤成長為 23 × 18 × 16 公分合併有縱膈腔向右偏移。病人在接受支持性療法後，死於多重器官衰竭。*(胸腔醫學 **2007; 22: 135-139**)*

關鍵詞：腸胃道基質瘤

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Severe Hypoxemia and Polycythemia due to Pulmonary Alveolar Microlithiasis — A Case Report

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Pulmonary alveolar microlithiasis (PAM) is a rare disease characterized by an intra-alveolar and interstitial accumulation of tiny, roundish corpuscles called ''microliths''. PAM may lead to hypoxemia, pulmonary hypertension (PH), respiratory failure and cor pulmonale. Lung transplantation is reserved for the extreme patient. We report a 27-year-old male presenting with shortness of breath for 5 years; his hemoglobin and hematocrit were 23.5 mg/dl and 68.6 vol%, respectively.

A pulmonary artery catheter revealed severe hypoxemia, PH, increased pulmonary vascular resistance, and a venous admixture. The chest X-ray showed a characteristic sandstorm pattern. High resolution computed tomography revealed diffuse micronodules and interlobar septal thickness. The bronchoalveolar lavage study disclosed characteristic concentric lamellar calcified microliths. The patient responded well to therapeutic phlebotomy and nasal continuous positive airway pressure. ***(Thorac Med 2007; 22: 140-145)***

Key words: pulmonary alveolar microlithiasis, dyspnea

Introduction

Pulmonary alveolar microlithiasis (PAM), first described by Feidirch in 1856, is a rare disease characterized by a progressive intra-alveolar formation and accumulation of laminated calcispherites in the absence of any known calcium metabolism disorder [1]. PAM evolves slowly, with a typical chest radiographic pattern showing diffuse, bilateral, medial and basal lung involvement [1]. The disease usually occurs in a sporadic form, but an autosomal recessive form has been described, especially in patients from the Mediterranean countries [2-4]. PAM is present on all continents.

Case Report

A 27-year-old truck driver, who had smoked 2 packs of cigarettes a day for 10 years, presented with a 5-year history of progressive shortness of breath on exertion. The dyspnea and dizziness were exacerbated by productive cough and fever in the most recent 3 days. Physical examination showed a 123 kg plethoric blue-collar worker with cyanosis on the lips and mucosa. Physical examination revealed blood pressure: 184/120 mmHg, heart rate: 80/min, respiration rate 22/

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min; bilateral wheezes and decreased breathing sounds in both lung fields; and a regular heart sound with no murmur. The blood cell count revealed elevated erythrocytes of $686 \times 10^4/mm^3$, Hb: 23.5 mg/dl and Hct: 68.6 Vol%. Arterial blood gas analysis values in room air were: pH: 7.425, PaO2: 46.3 mmHg, PaCO2: 23.5 mmHg, HCO3: 22.5 mmol/L, and O2 saturation 83.7%.

The pulmonary function test showed a moderate restrictive ventilatory defect with a reduced total lung capacity (TLC) of 57% and vital capacity (VC) of 56%, a forced expiratory volume in 1 sec/forced vital capacity (FEV1/FVC) of 86%, and a diffusing capacity (DLCO) of 13.1 ml/mmhg/min, 36% of predicted.

The chest X-ray (CXR) examination revealed a diffuse, symmetric, dense bilateral micronodular (''sand-storm'') pattern (Figure.1). High resolution computed tomography (HRCT) was performed to reveal inter-lobular septal thickening, subpleural interstitial thickening, and some ground glass opacity and micronodules (Figure 2). The picture was highly suspicious of PAM. Bronchoscopic examination showed normal mucosa, and bronchoalveolar lavage (BAL) harvested some clear bronchial fluid in which concentric lamellar calcified microlithes were observed (Figure 3). Pulmonary alveolar microlithiasis was diagnosed.

The patient's hypoxemia did not respond to 40% supplementary oxygen therapy. To further illuminate the oxygenation and hemodynamics, a pulmonary artery catheter was inserted, and revealed pulmonary artery pressure: 65/45 mmHg, pulmonary capillary wedge pressure: 21 mmHg, and cardiac output: 7.2l/min; calculated pulmonary vascular resistance (PVR): 363 dyn/cm^2 and SVR (systemic vascular resistance): 1437 dyn/cm^2; mixed vein oxygen saturation: 66%; and calculated veinous admixture: 45%.

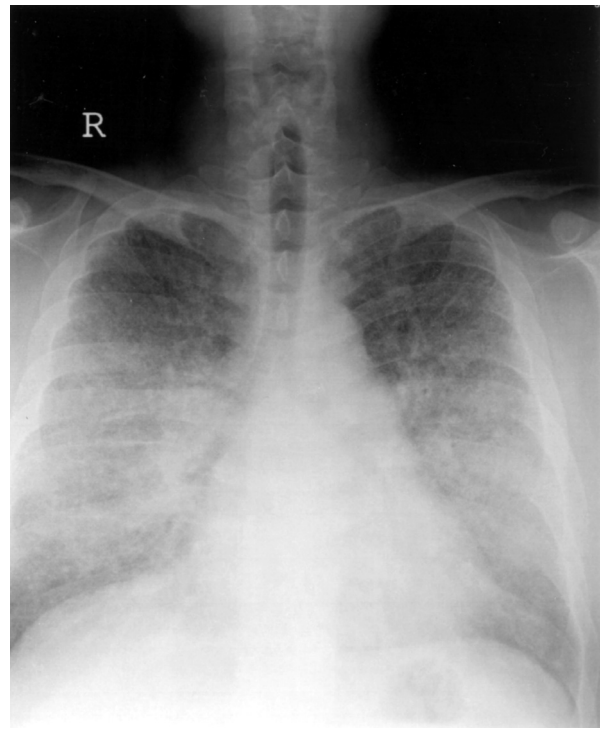
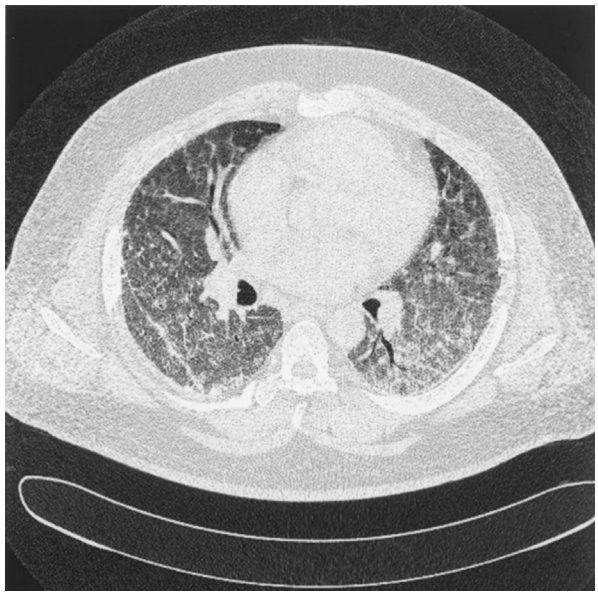


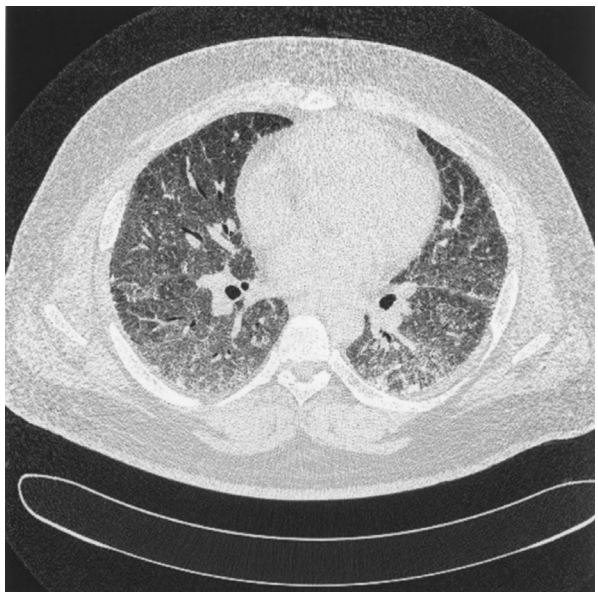
Fig. 1. CXR shows a bilateral diffuse, symmetric, dense micronodular (''sand-storm'') pattern, especially in the middle and lower lung fields (Initial).

Because of prolonged dizziness and refractory hypoxemia, a sleep study using polysomnography was performed. He had baseline pulse oxygen saturation (SpO2) of 82-84% in the awakened state, and when asleep, SPO2 dropped to around 66%, with the lowest point at 60%. The pulse rate fluctuated from 60 to 104 in response to hypoxemia. In addition, the patient's sleep was interrupted by repetitive arousals (17.7 events/hour) which were related to heavy snoring. The respiratory disturbance index (RDI) was 5.9 events/hour, which was compatible with mild sleep apnea. A nasal continuous positive airway pressure (CPAP) at 10 cmH2O restored SPO2 to 90%.

The patient received a phlebotomy 500 ml twice, and Hb decreased to 21.5 mg/dl. Dizziness and dyspnea improved after the phlebotomy. The



(A)



(B)

Fig. 2. HRCT images (2A, 2B) of a patient showing micro-nodules, sub-pleural interstitial thickening, inter-lobular septal thickening, and some ground glass opacity.

patient was discharged and received a nasal CPAP at 10 cm H2O. His Hb was maintained between 20 and 23 mg/dl during follow-up at our chest clinics. He continued working as usual as a truck driver.

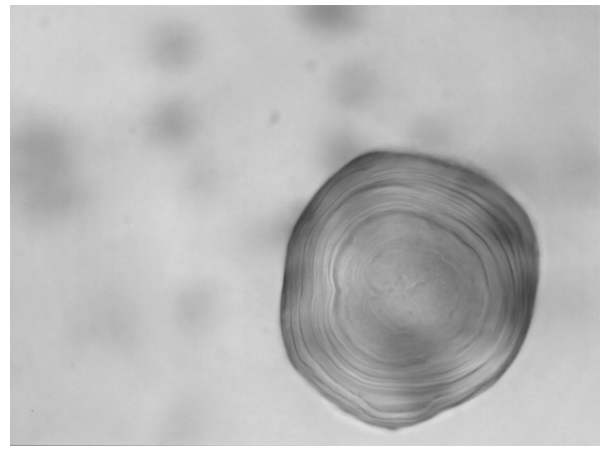


Fig. 3. BAL shows a laminated calcified microlith under microscopic examination. Hematoxylin & Eosin stain. 400X

Discussion

PAM is a rare idiopathic disease of unknown etiology and pathogenesis. About 500 cases have been reported worldwide, 60-65% of which were sporadic and showed a male prevalence, and 35-40% of which were familial cases with a female prevalence. The highest number of cases has been reported in Europe, followed by Asia, especially Asia Minor, while the individual nations with the greatest number of reported cases are Turkey, then Italy and the USA [6]. In Taiwan, there have been 2 reports of clusters of PAM [7-8].

The clinical course varies and does not correlate with CXR changes. Patients may remain asymptomatic for as long as 40 years, yet some become symptomatic within 10 years. Cough and dyspnea are the most common presenting symptoms and usually occur late in the course of the disease [1, 5]. The clinical presentation is usually of a lung disorder with a restrictive pattern [5, 9]. The lung function tests of this patient were compatible with the finding of the disease.

An isolated inborn error in calcium metabolism in the lungs has been proposed, but circulating calcium and phosphorus levels are consis-

tently normal in PAM. It is speculated that, due to an unknown stimulus, changes in the alveolar lining membrane or secretions result in greater alkalinity, promoting intra-alveolar precipitation of calcium phosphates and carbonates [10].

The CXR bilateral, sand-like, micronodular calcified densities known as microliths or calcispherites are usually less than 1 mm in diameter [9]. The predominant HRCT finding is the presence of micronodular calcifications primarily located along the bronchovascular bundles, and subpleural regions, with a perilobular distribution [5, 9]. The CXR and HRCT of our patient showed a typical pattern of pulmonary alveolar microlithiasis, just as the literature has demonstrated.

Histologically, the PAM lesion consists of intra-alveolar calcispherites, which represent laminated calcium phosphate concretions. Identification of microliths in expectorated sputum or BAL is diagnostic [10]. The BAL finding of a laminated calcified microlith in our patient thus confirmed the diagnosis.

The inability to identify clear etiological and pathogenetic elements makes the therapeutic approach difficult. The use of steroids has been proved to be ineffective, whereas therapeutic BAL fluid and diphosphonate have given rise to controversial opinions [5, 11]. Lung transplantation may be a treatment for PAM, but we do not know if PAM recurs after this procedure. If the disease results from a genetically determined error in the alveolar metabolism or local inflammatory response, recurrence would be unlikely. If the pulmonary disease is a manifestation of a systemic disorder, as in sarcoidosis and lymphangioleiomyomatosis, recurrence in the allograft is a possibility. The disease often takes many years to come to clinical attention, so more extended follow-up would be required to address this concern adequately [12]. In symptomatic cases, nasal continuous positive airway pressure (CPAP) improves gas exchange by decreasing the physiological intrapulmonary shunt [13]. In our patient, phlebotomy was performed to decrease the intravascular blood volume and blood viscosity related to over-compensating erythropoiesis. Dyspnea improved significantly after therapeutic phlebotomy. This may be another choice as a palliative treatment for PAM.

Severe hypoxemia and pulmonary hypertension have been observed in the late stage of PAM [5, 13]. This was assumed to be due to low V/Q or a shunt. The calculated veinous admixture, by assuming that the retardation of arterial oxygen transport comes entirely from the shunt, will overestimate it by adding to the low ventilation perfusion areas [13]. However, the 45% venous admixture in this patient reflected severe alveolar and interstitial deposition and functional deterioration. In addition, the beneficial effect of CPAP for hypoxemia in this patient also implicated the shunt mechanism in the pathogenesis of hypoxemia.

Polycythemia is defined by venous Hb greater than 18 grams/dl or venous Hct greater than 55%. The more severe the polycythemia is, the higher the resistance of the blood through the vasculature. The relationship of Hct and resistance is nearly linear below an Hct of 60%, but increases exponentially at an Hct approaching 70%. In this patient, the markedly increased PVR and mildly increased SVR were related to polycythemia. This was secondarily caused by hypoxemia, especially during sleep. The dyspnea and signs of heart failure were immediately relieved by phlebotomy.

In summary, the characteristic CXR and HRCT findings, combined with the clinical picture, are keys to the diagnosis of PAM. A BAL finding with laminated calcified microliths will confirm the diagnosis. Lung biopsy should be

avoided due to the risk of complications. There is no effective therapy for this disease, as yet. CPAP may be considered to improve the quality of life of these patients. Phlebotomy may be performed if significant erythrocytosis occurs.

References

1. Castellana G, Gentile M, Castellana R, *et al*. Pulmonary Alveolar Microlithiasis: Clinical Features, Evolution of the Phenotype, and Review of the Literature. American Journal of Medical Genetics 2002; 111: 220-4.
2. Esguerra G, Lichtemberger E, Santamaria A, *et al*. Familial pulmonary alveolar microlithiasis: four cases from Colombia, S.A.: is microlithiasis also an environmental disease? Radiology 1959; 72: 550-61.
3. Mariotta S, Guidi L, Papale M, *et al*. Pulmonary alveolar microlithiasis: review of Italian reports. Eur J Epidemiol 1997; 13: 587-90.
4. Ucan ES, Keyf AI, Aydilek R, *et al*. Pulmonary alveolar microlithiasis: review of Turkish reports. Thorax 1993; 48: 171-3.
5. Vito Michele Lauta. Pulmonary alveolar microlithiasis: an overview of clinical and pathological features together with possible therapies. Respiratory Medicine 2003; 97: 1081-5.
6. Castellana G, Lamorgese V. Pulmonary Alveolar Microlithiasis World Cases and Review of the Literature. Respiration 2003; 70: 549-55.
7. Chang YC, Yang PC, Luh KT, *et al*. High-resolution computed tomography of pulmonary alveolar microlithiasis. J Formos Med Assoc 1999; 98: 440-3.
8. Yang SP, Lin CC. Pulmonary alveolar microlithiasis: a case report of two youngest cases in a family. Disease of the Chest 1963; 44: 163-7.
9. Cluzel P, Grenier P, Bernadac P, *et al*. Pulmonary alveolar microlithiasis:CT findings. J Comput Assist Tomogra 1991; 15: 938-42.
10. Chan ED, Morales DV, Welsh CH, *et al*. Calcium Deposition with or without Bone Formation in the Lung. American Journal of Respiratory and Critical Care Medicine 2002; 165: 1654-69.
11. Gocmen A, Toppare MF, Kiper N, *et al*. Treatment of pulmonary alveolar microlithiasis with a diphosphonate: preliminary results of a case. Respiration 1992; 59: 250-2.
12. Edelman JD, Bavaria J, Kaiser LR, *et al*. Bilateral sequential lung transplantation for pulmonary alveolar microlithiasis. Chest 1997 Oct; 112(4): 1140-4.
13. Freiberg DB, Young IH, Laks L, *et al*. Improvement in gas exchange with nasal continuous positive airway pressure in pulmonary alveolar microlithiasis. Am Rev Respir Dis 1992; 145: 1215-6.

肺泡微結石症導致嚴重低血氧及紅血球增生—病例報告

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肺泡微結石症是一種罕見的肺部疾病，主要是在肺泡中產生細小圓形的細石沉積。肺泡微結石症可以導致低血氧，肺高壓，呼吸衰竭以及肺心症等臨床症狀。目前對症狀嚴重的病患，肺移植可能可以作為一個最後的選擇。我們報告一位 27 歲沒有任何系統性疾病的男性。五年前開始有輕微呼吸困難的現象，住院時的血色素為 23.5 mg/dl ，血容積為 68.6 Vol% 。

肺動脈導管顯示有嚴重低血氧，肺高壓，肺血管阻力上升。胸部 X 光有典型的沙暴型浸潤 (sandstorm)。肺部高解析度電腦斷層顯示許多細小結節以及葉間隔膜增厚。肺泡灌洗術的結果顯示典型的同心圓層狀鈣化微粒進一步確定診斷。病患的症狀在治療性放血以及連續正壓面罩使用之後顯著改善。*(胸腔醫學 **2007; 22: 140-145**)*

關鍵詞：肺泡微結石症，多血症，呼吸困難

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Melioidosis Mimicking Septic Embolism — A Case Report

Chia-Lin Lee, Chi-Huei Chiang

Melioidosis is infection with the Gram-negative bacterium *Burkholderia pseudomallei*. It is an important cause of sepsis in eastern Asia and northern Australia, and it often causes respiratory involvement and fatal fulminant septicemia. The mortality rate is high despite suggested therapy with ceftazidime, co-trimoxazole, amoxicillin-clavulanate, chloramphenicol, and tetracyclines. The number of documented cases in Taiwan has been increasing in recent decades, and melioidosis is regarded as an emerging infection. We report the case of a 52 year-old alcoholic male with diabetes who presented with severe left shoulder and left buttock pain, followed by respiratory symptoms. Chest radiograph and computed tomography disclosed findings mimicking septic embolism. A confirmed diagnosis of melioidosis was made via isolation of *B. pseudomallei* from the sputum and the blood sample. The patient was treated successfully with the combination of intravenous ceftazidime and trimethoprim-sulfamethoxazole, followed by maintenance therapy with oral levofloxacin. ***(Thorac Med 2007; 22: 146-152)***

Key words: melioidosis, *Burkholderia pseudomallei*, septic embolism, pneumonia

Introduction

Melioidosis is infection with the Gram-negative bacterium *Burkholderia pseudomallei*. It is an important cause of sepsis in eastern Asia and northern Australia. *B. pseudomallei* reside in water and wet soils, and mostly infect adults who are in a predisposing immunosuppressed state, such as patients with diabetes mellitus, renal disease, cirrhosis, thalassemia, or alcoholism [1]. In Taiwan, the reported cases of melioidosis have increased in number since 1985 [2]. Official reports from the Center of Disease Control in Taiwan suggest that outbreaks in the year 2001 may have been related to typhoons and flooding [3]. The mortality rate of septicemic melioidosis is high, even with suggested therapy with ceftazidime, co-trimoxazole, amoxicillin-clavulanate, chloramphenicol, and/or tetracycline [4]. Herein, we report the case of a patient with septicemic melioidosis with a clinical presentation of septic embolism who was treated successfully with intravenous ceftazidime and oral levofloxacin.

Case Report

A 52 year-old male, a heavy smoker who had consumed 40 cigarettes per day for 40 years, and

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a heavy drinker, who drank half a bottle of whiskey per day for 20 years, visited Penghu Naval Hospital in September 2005 due to fever and cough with scanty sputum for 4 days. He resided in the downtown area of Penghu County, and worked as a trash collector. He had empyema on the left side and had undergone surgery with decortication 3 years previously. General weakness struck 6 months before admission, and diabetes mellitus was diagnosed at that time. The patient underwent diet control and claimed a stable blood sugar level. The initial clinical presentation of this episode was severe pain in his left shoulder and left buttock area about 7 days prior to the development of respiratory symptoms. The patient was admitted and treated for pneumonia at Penghu Naval Hospital, but soon was referred to our hospital due to unresponsiveness to antibiotics therapy.

An initial physical examination at our hospital disclosed icteric sclera, diffuse crackles, hepatomegaly, and severe swelling with tenderness in the left shoulder and left buttock area. No local heat was detected and no other skin lesions were visible. Neither Murphy's sign nor flank knocking tenderness was detected. Laboratory investigations indicated significant leukocytosis (white blood cell count 17500/mm^3, neutrophils 83%), hyperbilirubinemia (total bilirubin level 3.6 mg/dl), and elevation of liver enzymes (alkaline phosphatase level 444 IU/L, normal range: 10-100 IU/L; alanine aminotransferase level 42 IU/L, normal range: 0-40 IU/L). The chest radiograph disclosed diffuse, patchy infiltrates in the bilateral lung fields. (Figure 1) Computed tomography of the chest disclosed ill-defined airspace consolidations mainly in the right upper lobe (posterior segment) and left upper lobe (anterior segment), and multiple subpleural ill-defined nodules in the bilateral upper and lower lung fields which mimicked septic emboli. (Figure 2) A gallium-67 inflammatory scan disclosed increased radioactivity in the left shoulder and left buttock area. (Figure 3) Abdominal echogram disclosed no focal lesions in the liver parenchyma,

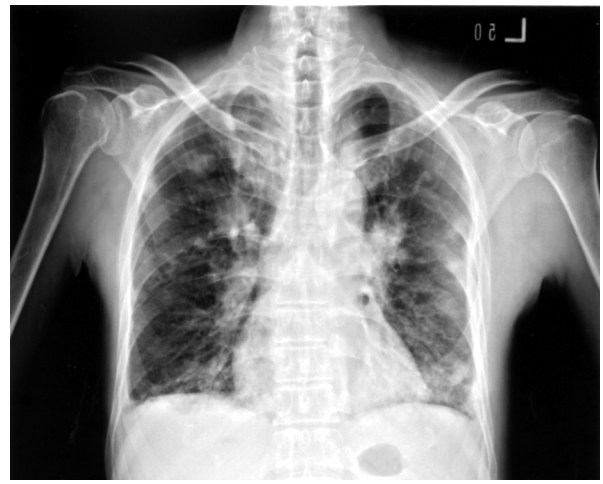


Fig. 1. Chest radiography at admission showing patchy pulmonary alveolar infiltrates in the bilateral upper and lower lung fields, nodules in the bilateral upper lung fields and small bilateral pleural effusions.

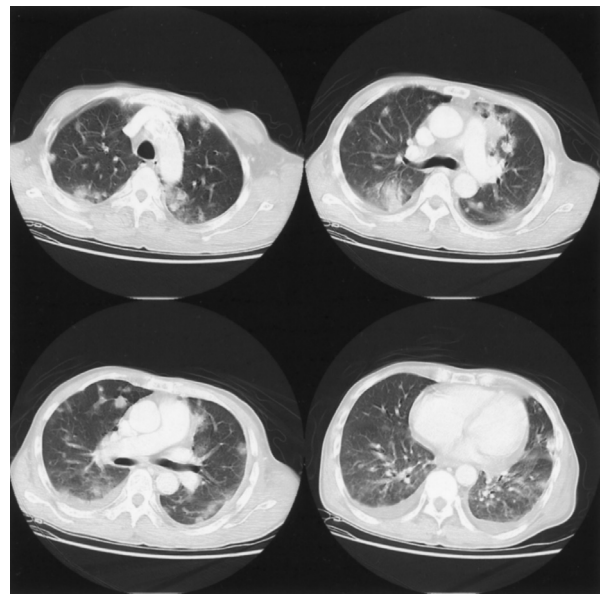


Fig. 2. Lung window of the chest computed tomography showing multiple subpleural nodules in the bilateral lung fields and patchy airspace consolidation and bilateral pleural effusions, suggesting septic embolism.

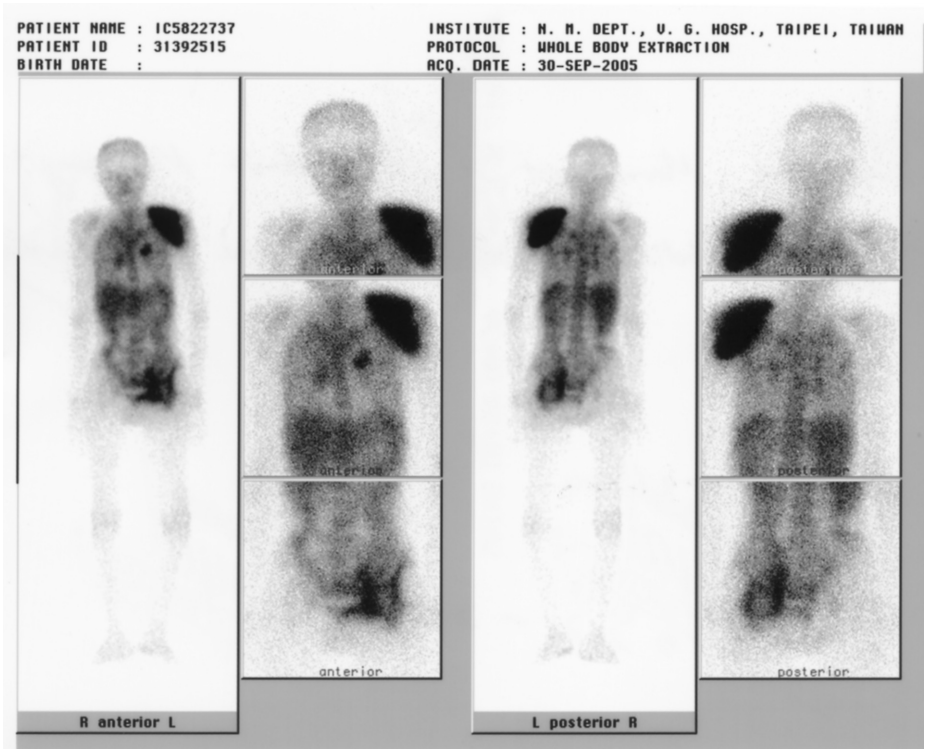


Fig. 3. The gallium 67 inflammation scan showing radioactivity in the left shoulder and left buttock region.

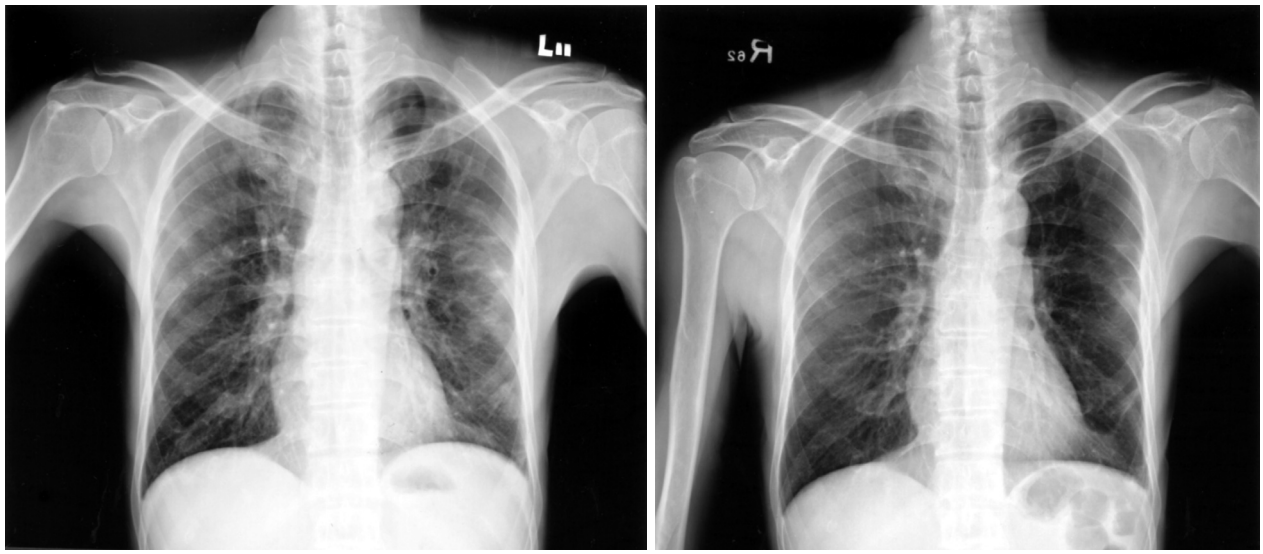
or evidence of cirrhotic change. Echocardiogram disclosed no evidence of vegetation.

Intravenous levofloxacin 500 mg per day was prescribed empirically. A sputum specimen and 2 sets of blood samples were sent for bacteria culture. All of them yielded *Burkholderia pseudomallei*, which was susceptible to ceftazidime, tetracycline, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole (TMP-SMX), ciprofloxacin and imipenem. Antibiotics therapy was then revised. Ceftazidime 2000 mg every 8 hours (120 mg/kg per day) and TMP-SMX 160/800 mg every 6 hours (TMP 12 mg/kg per day, SMX 60 mg/kg per day) were administered intravenously.

Fever and cough subsided after 7 days of antibiotics therapy. Resolution of swelling and tenderness of the left shoulder and left buttock area soon followed. The chest radiograph after 10 days of therapy disclosed a clearing of the bilateral lung fields. (Figure 4) After 24 days of intravenous antibiotics therapy, the patient was discharged with oral levofloxacin 500 mg per day. Maintenance therapy with oral levofloxacin was then administered continuously for 10 weeks at the outpatient service. The patient experienced no recurrence and presented no sequela after being followed up for 9 months.

Discussion

Melioidosis is endemic to Southeast Asia and northern Australia. Nearly all clinical studies have come from Thailand, Malaysia, Singapore, and northern Australia [5]. Reported outbreak episodes have been related to weather events, flooding or water supply problems. Increasing numbers of patients in the year 2005 in the southeast Pacific area indicated the relationship bet-



(A) (B)

Fig. 4. A series of chest radiographs showed responsiveness to antibiotics therapy. A) Chest radiograph taken after 10 days of antibiotics use showing partial resolution of pulmonary nodules and infiltrates. B) Chest radiograph taken 40 days after the diagnosis of melioidosis, showing only some linear infiltrates in the bilateral lung fields.

ween melioidosis and the tsunami in December 2004 [6]. Our patient worked as a trash collector, which might account for his contacting water or soil which contained *B. pseudomallei*. Being a diabetic and alcoholic made him vulnerable to such an infection.

Melioidosis usually presents as a febrile illness, ranging from an acute fulminant septicemia to a chronic debilitating localized infection, and typically forms abscesses. The majority of patients are septicemic, which is highly fatal. The mortality rate among adults in Thailand is about 50% [1]. The lung is the most commonly affected organ. Lung involvement may be the primary focus of infection or pneumonitis may be part of the multiorgan dissemination in patients with septicemia [7]. Chest radiographic changes include airspace consolidation, lung abscesses, nodular densities, sometimes with cavitation, and less commonly, pleural effusions. In a case review of melioidosis in Taiwan, 11 out of 15 cases presented with pneumonia [2]. The chest image study of our patient mimicked the findings of pulmonary septic embolism. This might be the result of fulminant septicemia.

Seeding and abscess formation can arise in any organ, although the liver, spleen, skeletal muscle, and prostate are common sites [1]. Though fulminant septicemia has occurred often, evidence of endocarditis was rarely documented [1]. Skin and soft tissue infections are a common manifestation of melioidosis [5]. Soft tissue infections may be the source of systemic infection or result from hematogenous spread. Soft tissue infections may be rapidly progressive and may mimic necrotizing fasciitis [5]. The initial presentations of our patient were severe pain and soft tissue swelling of the left shoulder and left buttock area. A skin defect might have been the entrance site for the bacteria in our patient, followed by hematogenous spreading of the bacteria to the lung. However, the patient could not recall any

trauma to his limbs.

The gold standard of diagnosing melioidosis is the isolation of *B. pseudomallei* from sputum, blood, urine, abscess fluid and throat swab samples [5]. Positive sputum cultures were associated significantly with the presence of renal impairment, respiratory symptoms or respiratory failure, abnormal chest radiographs, and throat swabs positive for *B. pseudomallei* [8]. Positive sputum cultures were thus thought to be associated with increasing mortality in patients with melioidosis.

Melioidosis is difficult to treat, and response to treatment is often disappointingly slow. Despite administration of a combination of 2 to 3 antibiotics or even high-dose parenteral antibiotics, mortality is still high [1]. The antibiotic of choice is ceftazidime [1]. Carbapenems kill *B. pseudomallei* more rapidly, and are widely used in Australia [1]. Cefoperazone-sulbactam has also proved effective. Intravenous amoxicillin-clavulanate, which needs to be given every 4 hours to ensure adequate trough levels of clavulanic acid, has been associated with similar mortality compared with ceftazidime, but a higher rate of relapse [5], though it is widely used in Thailand. Amoxicillin-clavulanate was then thought to be an appropriate empirical treatment in an endemic area, but treatment should be changed to ceftazidime or a carbapenem once the diagnosis of melioidosis has been confirmed [1]. Combination therapy with ceftazidime and TMP-SMX has resulted in a fall of the overall mortality in severe cases [5]. Conventional maintenance therapy consists of a 4-drug regimen (chloramphenicol, doxycycline, and TMP-SMX), which is commonly used in Thailand [1]. In northern Australia, monotherapy with co-trimoxazole is used for the maintenance phase [1]. In pregnant women or children, high doses of amoxicillin-clavulanate can be given as an alternative [1]. A combination of azithromycin and ciprofloxacin, which is better tolerated, but maybe less effective compared with the conventional regimen [1], may still be a viable choice of maintenance therapy [5]. In our case, the patient was treated initially with a combination of ceftazidime 120 mg/kg per day and TMP-SMX 12/60 mg/kg per day, which resulted in rapid resolution of the patient's symptoms. After that, a maintenance therapy with oral levofloxacin 500 mg per day was administered for 10 weeks. The reason for our choosing levofloxacin alone as maintenance therapy was its safety, good tolerance, and efficacy in treating soft tissue infections [9]. Though it may be less effective in treating melioidosis, its low rate of adverse effects and its convenience improve adherence. The risk of relapse is closely related to adherence to treatment and the initial extent of disease [1]. The treatment was proved effective with high adherence in our case, and resulted in no recurrence in the subsequent 9 months.

In conclusion, melioidosis, an emerging infection in Taiwan, often causes pneumonia, septicemia and abscesses. The mortality of septicemic melioidosis is high even with intensive care and suggested antibiotics therapy. On the other hand, melioidosis mimics other hematogenous suppurative diseases and can be misdiagnosed. Clinicians should be alert to the possibility of the disease when the patient presents with pneumonia, soft tissue infection, abscesses, and multiorgan involvement.

References

1. White NJ. Melioidosis [Seminar]. Lancet 2003; 361: 1715-22.
2. Hsueh PR, Teng LJ, Lee LN, *et al*. Melioidosis: An emerging infection in Taiwan? Emerg Infect Dis 2001; 7(3): 428-33.

3. Official Website of Center for Disease Control, R.O.C. (Taiwan) Http://www.cdc.gov.tw
4. Tsai W-C, Liu YC, Yen MY, *et al*. Septicemic melioidosis in Southern Taiwan: a case report. J Microbiol Immunol Infect 1998; 31(2): 137-40.
5. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. Clin Microbiol Rev 2005; 18(2): 383-416.
6. Chierakul W, Winothai W, Wattanawaitunechai C, *et al*. Melioidosis in 6 tsunami survivors in southern Thailand. Clin Infect Dis 2005; 41(7): 982-90.
7. Ip M, Osterberg LG. Pulmonary melioidosis. Chest 1995; 108: 1420-4.
8. Huis in't Veld D, Wuthiekanun V, Cheng AC, *et al*. The role and significance of sputum cultures in the diagnosis of melioidosis. Am J Trop Med Hyg 2005; 73(4): 657-61.
9. Blondeau JM. The role of fluoroquinolones in skin and skin structure infections. Am J Clin Dermatol 2002; 3(1): 37-46.

以敗血性血栓症爲臨床表現的類鼻疽—病例報告

李佳霖　江啟輝

類鼻疽 (Melioidosis) 是由類鼻疽伯克氏菌 (*Burkholderia pseudomallei*) 所感染造成的疾病。此病菌在東南亞及澳洲北部為相當重要的致病菌。類鼻疽經常造成肺部發炎性浸潤及嚴重的敗血症，而後者伴隨著相當高的死亡率。縱使合併使用多種有效的抗生素，死亡率仍居高不下。近年來，自此病被列為「傳染病個案報告單」之新增通報項目後，衛生單位已陸續接獲並證實有本土之散發性病例發生。

在此，我們報告一位 52 歲酗酒並罹患糖尿病的男性病人以左肩、左臀部疼痛及發燒、咳嗽來表現。一系列的胸部影像檢查疑似敗血性血栓症 (septic embolism)，而痰液及血液培養證實是類鼻疽。合併使用靜脈注射抗生素 ceftazidime (第三代頭孢子素) 及 trimethoprim-sulfamethoxazole (磺胺類藥物) 治療 24 天後，病人的臨床症狀及胸部 X 光得到迅速顯著的進步。繼之以口服 levofloxacin 10 週的加強治療。

在本文中，我們將進一步探討類鼻疽的臨床表徵，及治療用藥的選擇。*(胸腔醫學* ***2007; 22: 146-152****)*

關鍵詞：類鼻疽，類鼻疽伯克氏菌，敗血性血栓症，肺炎

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