Specific Allergen Tests in Asthmatic Patients: A Comparison Between Adults and Children

Chia-Lin Hsu, Bor-Luen Chiang*, Sow-Hsong Kuo

Background: The prevalence of asthma is increasing gradually in Western countries as well as in the Far East. Environmental factors have been proposed as one of the reasons for the wide variations in asthma epidemiology. In this study, we investigated the differences in specific allergen tests between asthmatic children and adults, and the relationship between specific allergen tests and total serum immunoglobulin E (IgE) and peripheral blood eosinophilia.

Methods: A total of 68 adults and 55 children who were diagnosed with asthma at our outpatient department were enrolled in this study. All patients underwent a specific allergen test measured by multiple allergosorbent chemiluminescent assay (MAST-CLA). Based on the results of the MAST-CLA test, patients were divided into two groups. The MAST (+) group was defined as patients having at least one positive allergen in their MAST-CLA test. Eosinophil counts greater than 300/μL were defined as eosinophilia. An elevated total IgE level was defined as a total IgE level of more than 200kU/L in adults, and was adjusted for age in children.

Results: Forty-nine (72.1%) adults and 36 (65.5%) children were MAST (+). In the MAST (+) group, a higher allergen number was noted in asthmatic children than in adults (4.8 ± 3.5 vs. 3.5 ± 2.0, p=0.04). The children had a higher incidence of food allergens than adults (n=18, 32.7% vs. n=11, 16.2%, p=0.03), especially to milk (n=15, 27.3% vs. n=1, 1.5%, p<0.001). In the adult patients, the allergen number was correlated to total IgE level (r=0.85, p<0.001), but not to eosinophil count. In the children, the allergen number was correlated well to the total IgE level (r=0.82, p<0.001) and eosinophil count (r=0.60, p=0.001).

Conclusion: The positive tendency in the MAST-CLA test was similar in both adults and children, but the positive tendency to food allergens was significantly higher in children. In the MAST (+) group, children had more allergens than adults. The allergen number was correlated to the peripheral blood eosinophil count and the level of total serum IgE in the asthmatic children.
(Thorac Med 2004; 19: 82-91)

Key words: asthma, specific allergen test, immunoglobulin E, eosinophil

Introduction

The prevalence of asthma is gradually increasing in Western countries as well as the Far East, including Taiwan [1-4]. The prevalence of self-reported wheezing varies from 3.1% to 13.2% (4.2% in 13- to 14-year-old children in Taiwan) among Chinese-speaking children in the countries

Department of Internal Medicine, National Taiwan University Hospital, and *Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan
Address reprint requests to: Dr. Sow-Hsong Kuo, Department of Internal Medicine National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan

of Southeast Asia [5]. Many factors involved in the pathophysiology of asthma and the exact reason for the increase in prevalence is still unknown. Differences in environmental factors have been proposed as one of the reasons for the wide variation in asthma epidemiology.

It is generally accepted that non-allergic asthma can be objectively distinguished from allergic asthma by the absence or presence of allergy skin test reactivity to one or more aeroallergens considered capable of inducing the disease [6]. Experimental and clinical studies have provided evidence for the role of allergy in the development of airway responsiveness. Most asthmatic patients, especially children, have clinical features of atopy, including eczema, rhinitis and a positive skin-prick test (SPT) with elevated immunoglobulin E (IgE) levels [7]. Skin reactivity in early childhood was also found to be a predictor of the late appearance of bronchial hyper-responsiveness (BHR) [8]. In adult patients, BHR is more prevalent among those with a positive SPT [9], increased serum total IgE or specific IgE levels [10-11], and peripheral blood eosinophilia [12].

In Taiwan, previous studies had shown that different common allergens occur in different age groups of asthmatic patients [13-14]. Among aeroallergens, mite allergy occurred more frequently in 11-20-year-old patients. Among food allergens, milk and egg white allergens were found more frequently in 1-10-year-old patients. However, there is a paucity of data on the difference in complete specific allergen tests, total IgE, and peripheral blood eosinophilia between children and adults with asthma. In this study, we investigated the differences in specific allergen tests (measured by multiple allergosorbent chemiluminescent assay, MAST-CLA) in asthmatic children and adults, and tried to find the relationship between a specific allergen test and IgE, and peripheral blood eosinophilia.

Methods

Patients

From July 2000 to December 2002, asthmatic patients who underwent a multiple allergosorbent chemiluminescent assay (MAST-CLA) at the outpatient department of National Taiwan University Hospital were enrolled. In the adult patients (age ≥ 16 years), asthma was diagnosed according to the GINA (Global Initiative for asthma) guidelines [15]. Among the children (age < 16 years), patients were diagnosed with asthma if they had frequent wheezing episodes with dyspnea or exercise intolerance. Allergic rhinitis was diagnosed by physicians based on clinical features (frequent rhinorrhea, nasal obstruction and boggy nasal mucosa). Severity of asthma in the adults was classified based on the GINA guidelines and presented as class 1 (mildly intermittent) to 4 (severely persistent) [15].

MAST-CLA

The multiple allergosorbent chemiluminescent assay (MAST-CLA, Hitachi Chemical Diagnostics, Inc, Japan) is a test for the simultaneous measurement of total IgE and specific IgE directed against 36 different allergens (Table 1), including 16 food allergens, in a single tube (pette). The patient's blood sample is drawn and the serum is separated and aspirated into the test chamber followed by a buffer wash. A secondary antibody, anti-human IgE-HRP (polyclonal anti-IgE antibody conjugated to horseradish peroxidase, Hitachi Chemical Diagnostics, Inc, Tokyo), is incubated followed by a second buffer wash. The substrate is a chemiluminescent reagent. The luminescent signal is read in a chemiluminescent analyzer (CLA-1, Hitachi Chemical Diagnostics, Inc, Tokyo) to determine the concentration of IgE specific antibodies attached to the solid phase.

Data Collection

The medical records of these patients were analyzed for age, gender, the presence of allergic rhinitis, and the severity of asthma. Patients were divided into two groups based on the results of their MAST-CLA tests. The MAST (+) group was composed of patients with at least one positive allergen in the MAST-CLA test. The MAST (-) group con-

sisted of those in whom no allergen was detected in the MAST-CLA test. The pulmonary function test and blood eosinophil counts within one month of the MAST-CLA test were also collected. Due to poor cooperation, most of the children did not undergo a pulmonary function test. Eosinophilia was defined as an absolute eosinophil count of more than 300/μL. Elevated total IgE was defined as > 200 kU/L in adults and children aged over 10 years. In the children, the normal value of total IgE was adjusted by age (1 year: 29.2; 2 years: 51.7; 3 years: 72; 4 years: 90; 5 years: 108; 6 years: 126; 7 years: 142; 8 years: 160; 9 years: 176; 10 years: 192) [16].

Statistical Analysis

Data is expressed as mean ± standard deviation (continuous variables) or as a percentage of the group from which they were derived (categorical variables). Differences in positive and negative MAST-CLA subgroups of variables, including total IgE, absolute blood eosinophil count, FEV_1 percentage of the predicted value, FVC percentage of the predicted value, and FEV_1/FVC, were analyzed by independent *t*-test. The subgroups of allergic rhinitis, eosinophila, and elevated IgE were analyzed by Chi-square test. Correlations between the two continuous variables were analyzed by Pearson bivariate correlation test. A p value of 0.05 or less was considered significant.

Results

A total of 68 adults and 55 children were enrolled in this study. The mean age was 41.4 years (range: 16-76 years) for adults and 6.9 years (range: 3-15 years) for children. The male/female gender ratio was 30:38 in adults and 39:16 in children (p= 0.004). The children suffered more allergic rhinitis than the adults (81.8% vs. 47.1%, p<0.001, Table 2). A positive MAST was found in 49 (72.1%) adults and 36 (65.5%) children. The total serum IgE level was checked in 26 adults and 45 children, with a mean value of 382 ± 513 kU/L and 414 ± 523 kU/L, respectively. Eosinophil counts in the peripheral blood were examined in 34 adults and 37 children, with a mean value of 387 ± 323 /μL and 443 ± 385 /μL, respectively. No differences in positive MAST, eosinophil counts, or total IgE were noted between the adults and children (Table 2).

The mean number of allergens was 2.5 ± 2.4 and 3.1 ± 3.6 in the adults and children, respectively (p=0.11). The distribution of allergen numbers in

Table 1. Specific allergens in the MAST-CLA test

Foods		**Molds**	**Animal epidermals**
Citrus mix	Pork	Alternaria	Feather mix
Corn	Beef	Aspergillus	Cat
Wheat	Milk	Candida	Dog
Vegetable mix	Yeast, Brewer's	Cladosporium	
Crab	Soybean	Penicillium	
Shellfish mix	Peanut		**Insect**
Shrimp	Egg yolk		Cockroach mix
Codfish	Egg white		
Trees	**Grasses/Weeds**	**Household dust and mites**	
Pine mix	Grass mix	Household dust	
Cottonwood/Willow	Bermuda grass	Dermatophagoides pteronyssimus	
Eucalyptus	Ragweed mix	Dermatophagoides farinae	
Mulberry mix	Pigweed mix		

MAST-CLA: Multiple allergosorbent chemiluminescent assay

Table 2. Clinical characteristics of asthmatic adults and children

	Adult (n=68)	Children (n=55)	*p*-value
Gender (M/F)	30/38	39/16	0.004
Age (yr)	41.4 ± 14.6	6.9 ± 2.6	<0.001
Allergic rhinitis	32 (47.1%)	45 (81.8%)	<0.001
MAST (+)	49 (72.1%)	36 (65.5%)	0.43
Number of allergens	2.5 ± 2.4	3.1 ± 3.6	0.11
Positive food allergens	11 (16.2%)	18 (32.7%)	0.03
Number of food allergens	0.4 ± 1.2	0.9 ± 2.2	0.04
Eosinophils (/μL)	387 ± 323	443 ± 385	0.80
Total IgE (kU/L)	382 ± 513	414 ± 523	0.80

Data represented by mean ± SD. Total IgE: total serum immunoglobulin E

MAST (+) patients is demonstrated in Figure 1. The positive rate of food allergens was 16.2% in adults and 32.7% in children (p=0.03, Table 2). Figure 2 illustrates the distribution of food allergen numbers. The three most common allergens in both adults and children were Dermatophagoides farinae, Dermatophagoides pteronyssinus, and household dust (Table 3). The most common food allergens in the adults were shrimp (11.8%), crab (7.4%) and shellfish (7.4%). The most common food allergens in children were milk (27.3%), shrimp (14.5%), crab

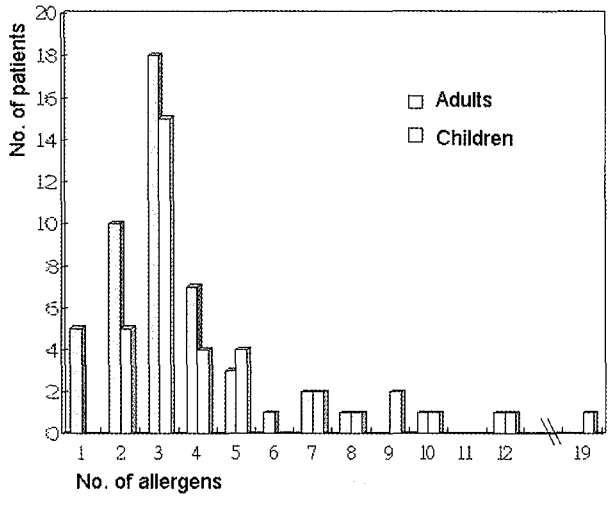

Fig. 1. Number of allergens in MAST (+) adults and MAST (+) children. (MAST (+): at least one positive allergen in the MAST-CLA test)

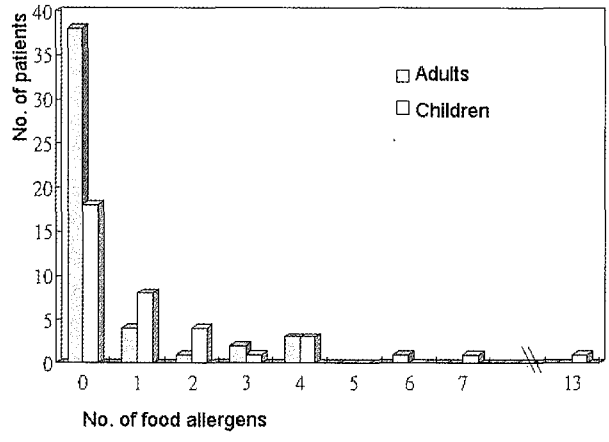

Fig. 2. Number of food allergens in MAST (+) adults and MAST (+) children. (MAST (+): at least one positive allergen in the MAST-CLA test)

(9.1%) and egg whites (9.1%). Compared to the adults, milk was the most important food allergen in children (27.3% vs. 1.5%, p<0.001). In the MAST (+) group, more allergens were noted in children than in adults (4.8 ± 3.5 vs. 3.5 ± 2.0, p=0.04), but there were no differences in eosinophil counts and total serum IgE levels between the adults and children.

In the adults, there was no significant difference in gender, age, and allergic rhinitis between the MAST (+) and MAST (-) groups (Table 4). Variants in eosinophil count, eosinophilia, total IgE, FVC%, FEV_1/FVC, and severity of asthma also did not differ between the two groups (Table 4). More adult

Table 3. Comparison of common allergens between adults and children

Allergen	Adults (n=68)		Children (n=55)		*p*-value
Dermatophagoides farinae	43	(63.2%)	35	(63.6%)	0.96
Dermatophagoides pteronyssimus	39	(57.4%)	35	(63.6%)	0.48
Household dust	30	(44.1%)	27	(49.1%)	0.58
Cockroach mix	12	(17.6%)	10	(18.2%)	0.94
Dog	9	(13.2%)	6	(10.9%)	0.70
Shrimp	8	(11.8%)	8	(14.5%)	0.65
Shellfish mix	5	(7.4%)	3	(5.5%)	0.67
Crab	5	(7.4%)	5	(9.1%)	0.73
Cat	4	(5.9%)	3	(5.5%)	0.92
Codfish	3	(4.4%)	1	(1.8%)	0.42
Vegetable mix	3	(4.4%)	1	(1.8%)	0.42
Egg white	2	(2.9%)	5	(9.1%)	0.14
Milk	1	(1.5%)	15	(27.3%)	< 0.001
Soybean	1	(1.5%)	3	(5.5%)	0.22

patients with elevated total serum IgE (73.7% vs. 14.3%, p=0.007) and higher FEV_1% (83.8 ± 19.5% vs. 72.1 ± 21.3%, p=0.04) were noted in the MAST (+) group than in the MAST (-) group (Table 4). Among the children, there was no difference in the incidence of allergic rhinitis between the MAST (+) and MAST (-) groups (Table 5). Compared to the MAST (-) children, significantly more male, older average age, higher eosionophil counts, higher total serum IgE, and more elevated IgE subjects were noted in the MAST (+) group (Table 5).

In the children, the allergen number correlated well with the eosinophil counts (r=0.60, p=0.001), (Figure 3) and total serum IgE levels (r=0.82, p< 0.001), (Figure 4). The total serum IgE levels were also correlated to the eosinophil counts (r=0.54, p=0.001). On the other hand, the allergen number was correlated well only with total serum IgE levels (r=0.85, p<0.001), (Figure 4), and not with eosinophil counts in adults. Higher total IgE levels and

Table 4. Comparison of MAST (+) and MAST (-) groups of asthmatic adults

	MAST (+) (n=49, 72.1%)	MAST (-) (n=19, 27.9%)	*p*-value
Gender (M/F)	24/25	6/13	0.20
Age (yr)	39.4 ± 14.3	46.4 ± 14.6	0.08
Allergic rhinitis	26/49 (53.1%)	6/19 (31.6%)	0.11
Eosinophil count (/μL)	391.5 ± 329.7	373.7 ± 324.4	0.89
Eosinophilia	13/25 (52%)	5/9 (56%)	0.86
Total IgE (kU/L)	474 ± 562	131 ± 216	0.13
Elevated IgE	14/19 (73.7%)	1/7 (14.3%)	0.007
FEV_1% predicted	83.8 ± 19.5%	72.1 ± 21.3%	0.04
FVC% predicted	99.0 ± 18.4%	90.7 ± 15.8%	0.10
FEV_1/FVC (%)	73.6 ± 11.9%	66.9 ± 14.9%	0.07
Asthma severity	2.3 ± 0.8	2.4 ± 0.9	0.61

Data represented by mean ± SD. MAST (+): at least one positive allergen in the MAST-CLA test, Eosinophilia: >300/μL, Total IgE: total serum immunoglobulin E, Elevated IgE: Immunoglobulin E > 200kU/L

Table 5. Comparison of MAST (+) and MAST (-) groups of asthmatic children

	MAST (+) (n=36, 65.5%)	MAST (-) (n=19, 34.5%)	*p*-value
Gender (M/F)	29/7	10/9	0.03
Age (yr)	7.6 ± 2.9	5.6 ± 1.4	0.006
Allergic rhinitis	29/36 (80.6%)	16/19 (84.2%)	0.74
Eosinophil count (/μL)	559 ± 437	254 ± 163	0.02
Eosinophilia	15/23 (65.2%)	5/14 (35.7%)	0.08
Total IgE (kU/L)	588 ± 578	101 ± 123	0.002
Elevated IgE	24/29 (82.8%)	4/16 (25.0%)	0.001

Data represented by mean ± SD. MAST (+): at least one positive allergen in the MAST-CLA test, Eosinophilia: >300/μL, Total IgE: total serum immunoglobulin E; Elevated IgE: Immunoglobulin E beyond the normal range adjusted by age

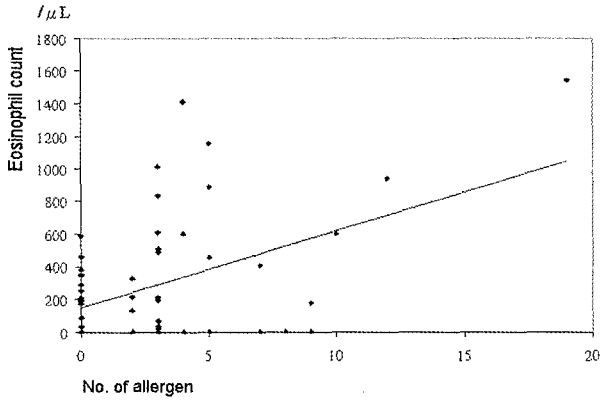

Fig. 3. Correlation of allergen number and eosinophil count in asthmatic children (r=0.60, p=0.001)

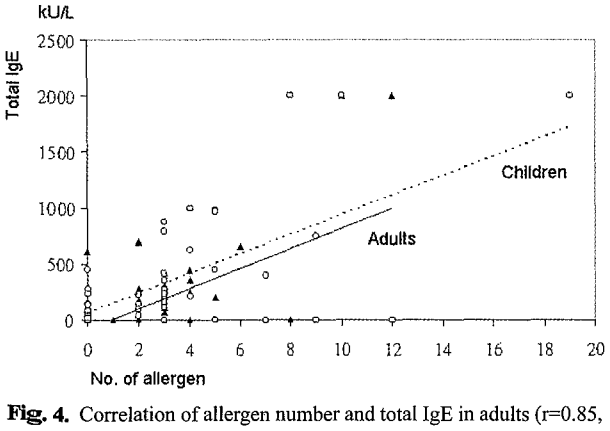

Fig. 4. Correlation of allergen number and total IgE in adults (r=0.85, p<0.001) and children (r=0.82, p<0.001) (▲ adult, ○ children)

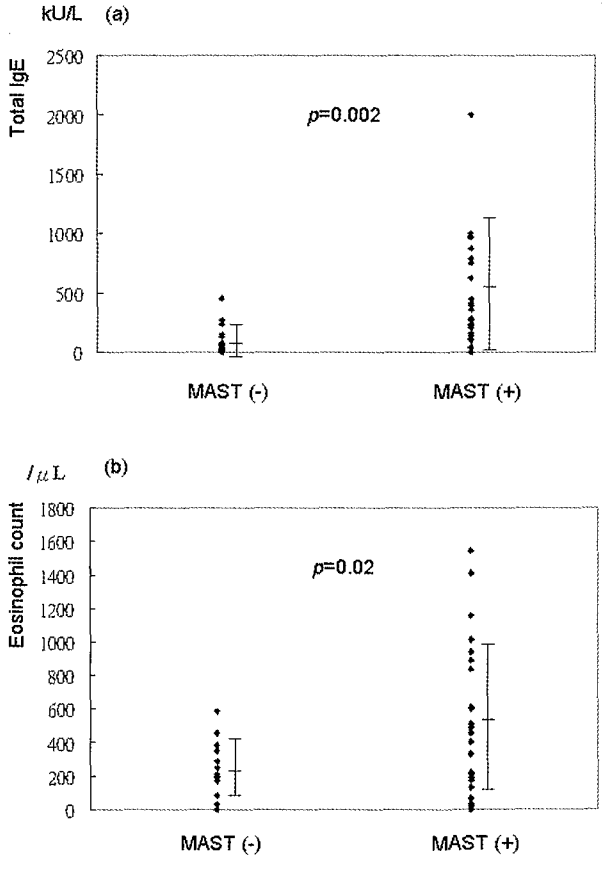

Fig. 5. Comparison of (a) total IgE level and (b) eosinophil count between the MAST (-) and MAST (+) groups of children. The horizontal bars depict the mean value and SD. MAST (+): at least one positive allergen in the MAST-CLA test

more eosinophil counts were noted in the MAST (+) children than in the MAST (-) children (Figure 5a, b), but there were no significant differences between the MAST (+) and MAST (-) adults (Table 4).

Discussion

In this study, the clinical characteristics and laboratory data of the adults and children were similar, except that the children had a higher prevalence of allergic rhinitis and were predominantly male. As in other studies [17-18], asthma was more common in boys than girls, and the gender difference disappeared during early adulthood [17,19]. Allergic rhinitis and bronchial asthma frequently coexist, and are reported in from 28% to 78% of patients with asthma [20-21]. Our study revealed a high incidence (81.8%) of allergic rhinitis in asthmatic children – this could indicate an over-diagnosis connected to non-allergic rhinitis. Adult patients had a higher prevalence of positive MAST tests and lower allergen numbers compared with the children, but there were no significant differences. The higher allergen number in children resulted from higher incidences of food allergens.

Our study demonstrated the differences between the MAST (+) and MAST (-) groups of asthmatic adults and children. The allergen number was well correlated to the total serum IgE levels and peripheral blood eosinophils in the children. In the MAST (+) group, we found that children might be sensitive to more allergens, and had a higher incidence of food allergens. Except for food allergens, the number of other sensitive allergens - including inhaled allergens, fungus, and pollen, were similar between the asthmatic adults and children. Tsai et al. reported that milk, egg white, and Dermatophagoides pteronyssinus allergens were more prevalent in children or adolescents than in adult patients [13-14]. Lee et al. reported that crab, milk, and egg whites were the most prevalent food allergens in 2-6-year-old children with allergic disease in Taiwan [22]. Our observations were similar. That the incidence of egg white and Dermatophagoides pteronyssinus allergens showed no difference between the adults and children in this study might be due to the relatively small case number. Our study showed a much higher incidence of milk allergy in children than in adults (27.3% vs. 1.5%, $p<0.001$). The incidence of milk allergy in infancy was reported to be 2%-3%, with a remission rate of 85%-90% before the age of 3 [23]. This might be the reason that only one adult had a milk allergy in this study.

In the adult patients, the MAST (+) group showed a higher FEV_1% predicted value and a higher incidence of elevated IgE than the MAST (-) group. Similar results were also noted in previous studies in which negative SPT asthmatic patients had poorer lung function and more severe symptoms than those with positive SPT [24-25]. In contrast, another study did not find SPT to be related to FEV_1 nor to asthma severity [26]. This result, witnessed in clinical practice, has not been clearly demonstrated so far. Good correlations between allergen number and total IgE levels were noted in both adults and children. The correlation of allergen number and eosinophil count was found only in the children. The allergen challenge might increase the local concentration of interleukin-5, which correlates directly with airway eosinophilia and stimulates the release of eosinophils into the circulation, prolonging their survival [27-28]. This might be the reason that the allergen number correlates to the eosinophil count. Silvestri et al. also showed that allergen-induced T-lymphocyte proliferation is related to the serum IgE level and blood eosinophilia [29]. The degree of T-lymphocyte proliferation depends on the intensity of allergen exposure.

In children, the MAST (+) group had a higher eosinophil count and higher total serum IgE level than the MAST (-) group. The parameters of positive SPT, eosinophilia, and high total IgE levels have been shown to correlate with BHR or asthma [6, 9-12]; but, the positive rate of all three measures (SPT, serum IgE, and eosinophil) in the same patients was from 1.5% to 48% [30-31]. This means that the three measures were different expressions of the atopic phenotype. No correlation was noted between the allergen numbers and eosinophil counts in adults, which might be due to the different immune expressions in different examinations.

In conclusion, children might have more allergens, especially food allergens, compared to adults in the MAST (+) group. A higher incidence of eosinophilia and elevated total IgE serum levels

were found in MAST (+) children than MAST (-) children. The allergen number in the MAST had a good correlation with the level of total serum IgE in both adults and children.

References

1. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years part. Br Med J 1992; 304: 873-5.
2. Burr ML, Butland BK, King S, *et al.* Changes in asthma prevalence: two surveys 15 years apart. Arch Dis Child 1989; 64: 1452-6.
3. Hsieh KH, Shen JJ. Prevelance of childhood asthma in Taipei, Taiwan, and other Asian Pacific countries. J Asthma 1988; 25: 73-82.
4. Lai CK, Douglass C, Ho SS, Chan J, Lau J, Wong G, Leung R. Asthma epidemiology in the Far East. Clin Exp Allergy 1996; 26: 5-12.
5. Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. J Allergy Clin Immunol 2000; 105: S466-72.
6. Burrows B, Martinez FD, Halonen M, *et al.* Association of asthma with serum IgE levels and skin test reactivity to allergens. N Engl J Med 1989; 320: 271-7.
7. Busse WW, Lemanske RF. Advances in immunology: asthma. N Engl J Med 2001; 344: 350-62.
8. Cartier A, Thrompson NC, Frith PA, *et al.* Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. J Allergy Clin Immunol 1982; 70: 170-7.
9. Britton J, Pavord I, Richards K, *et al.* Factors influencing the occurrence of airway hyperreactivity in the general population: the importance of atopy and airway calibre. Eur Respir J 1994; 7: 881-7.
10. Omenaas E, Bakke P, Eide GE, *et al.* Serum house dust mite antibodies: predictor of increased bronchial responsiveness in adults of a community. Eur Respir J 1996; 9: 919-25.
11. Sunyer J, Munoz A. Concentrations of methacholine for bronchial responsiveness according to symptoms, smoking and immunoglobulin E in a population-based study in Spain. Spanish Group of the European Asthma Study. Am J Respir Crit Care Med 1996; 153: 1273-9.
12. Taylor KJ, Luksza AR. Peripheral blood eosinophil counts and bronchial responsiveness. Thorax 1987; 42: 452-6.
13. Tsai JJ, Chen WC. Different age of asthmatic patients affected by different aeroallergens. J Microbiol Immunol Infect 1999; 32: 283-8.
14. Tsai JJ, Chen WC. Relation of different food allergens to different age of asthmatic patients. J Microbiol Immunol Infect 1999; 32: 47-51.
15. National Heart Lung and Blood Institute, World Health Organization Global Initiative for Asthma. Global strategy for asthma management and prevention: NHLBI/WHO workshop report. 1995; 1-176.
16. Johansson SG, Yman L. In vitro assays for immunoglobulin E. Methodology, indications, and interpretation. Clin Rev Allergy 1988; 6: 93-139.
17. Venn A, Lewis S, Cooper M, *et al.* Questionnaire study of effect of sex and age on the prevalence of wheeze and asthma in adolescence. Br Med J 1998; 316: 1945-6.
18. El-Sharif NA, Nemery B, Barghuthy F, *et al.* Geographical variations of asthma and asthma symptoms among school children aged 5 to 8 years and 12 to 15 years in Palestine: the International Study of Asthma and Allergies in Childhood (ISAAC). Ann Allergy Asthma Immunol 2003; 90: 63-71.
19. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992; 47: 537-42.
20. Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. Allergy 1983; 38: 25-9.
21. Corren J. Allergic rhinitis and asthma: how important is the link? J Allergy Clin Immunol 1997; 99: S781-6.
22. Lee CS, Tang RB, Chung RL. The evaluation of allergens and allergic diseases in children. J Microbiol Immunol Infect 2000; 33: 227-32.
23. Host A. Frequency of cow's milk allergy in childhood. Ann Allergy Asthma Immunol 2002; 89: 33-7.
24. Ulrik CS, Backer V, Dirksen A. A 10-year follow-up of 180 adults with bronchial asthma: factors important for the decline in lung function. Thorax 1992; 47: 14-8.
25. Romanet-Manent S, Charpin D, Magnan A, *et al.* Allergic vs nonallergic asthma: what makes the difference? Allergy 2002; 57: 607-13.
26. Cline MG, Dodge R, Lebowitz MD, *et al.* Determinants of percent predicted FEV_1 in current asthmatic subjects. Chest 1994; 106: 1089-93.
27. Sedgwick JB, Calhoun WJ, Gleich GJ, *et al.* Immediate

and late airway response of allergic rhinitis patients to segmental antigen challenge. Characterization of eosinophil and mast cell mediators. Am Rev Respir Dis 1991; 144: 1274-81.

28. Sanderson CJ. Interleukin-5, eosinophils, and disease. Blood 1992; 79: 3101-9.
29. Silvestri M, Oddera S, Spallarossa D, *et al.* In childhood asthma the degree of allergen-induced T-lymphocyte proliferation is related to serum IgE levels and to blood eosinophilia. Ann Allergy Asthma Immunol 2000; 84: 426-32.
30. Jansen DF, Rijcken B, Schouten JP, *et al.* The relationship of skin test positivity, high serum total IgE levels, and peripheral blood eosinophilia to symptomatic and asymptomatic airway hyperresponsiveness. Am J Respir Crit Care Med 1999; 159: 924-31.
31. Khadadah M, Onadeko BO, Ezeamuzie CI, *et al.* The association of skin test reactivity, total serum IgE levels, and peripheral blood eosinophilia with asthma in Kuwait. J Asthma 2000; 37: 481-8.

兒童及成人氣喘患者之特定過敏原測試比較

許嘉林　江伯倫*　郭壽雄

背景：氣喘發生率於西方國家及遠東地區都有逐漸增加之情形，而環境因子被認為是影響氣喘流行病學的因素之一。本研究探討特殊過敏原測試於兒童及成人氣喘病患之差異，及過敏原與免疫球蛋白 E 及週邊血液嗜伊紅白血球之相關性。

方法：本研究自西元 2000 年 7 月至西元 2002 年 12 月於臺大醫院門診收集 68 位成人及 55 位兒童氣喘患者。所有的病患都接受過特定過敏原測試(MAST-CLA)，且依據測試結果分成兩組。過敏原測試陽性(MAST +)定義為至少對一種或一種以上之過敏原有反應；其餘病患則歸為過敏原測試陰性。嗜伊紅白血球過高定義為週邊血液嗜伊紅白血球超過 300/ 閎；而免疫球蛋白 E 之成人標準值設定為 200kU/L ，兒童則依照年齡加以調整。

結果：共有 49 位(72.1%)成人及 36 位(65.5%)兒童於特殊過敏原測試呈陽性反應。在 MAST(+)之病患中，兒童所測試出之過敏原數目高於成人(4.8 ± 3.5 vs. 3.5 ± 2.0, p=0.04)。與成人相較，兒童對食物過敏原有較高之陽性率(兒童 18 人, 32.7% vs. 成人 11 人, 16.2%, p=0.03)，尤其以牛奶最為明顯(兒童 15 人, 27.3% vs. 成人1人, 1.5%, p<0.001)。在成人病患，過敏原數目僅與免疫球蛋白E之濃度有正相關(r=0.85, p<0.001)；而在兒童病患，過敏原數目則與免疫球蛋白 E (r=0.82, p<0.001)及嗜伊紅白血球(r=0.60, p=0.001)皆有正相關。

結論：於過敏原測試呈陽性反應之病患中，兒童相較於成人，對較多種過敏原呈陽性反應。過敏原之數目，在成人與免疫球蛋白 E 之濃度有相關；在兒童則與免疫球蛋白 E 及嗜伊紅白血球皆有相關。*(胸腔醫學 2004; 19: 82-91)*

關鍵詞：氣喘，特殊過敏原測試，免疫球蛋白 E ，嗜伊紅白血球

國立台灣大學附設醫院　內科部　國立台灣大學醫學院　臨床研究所 *
索取抽印本請聯絡：郭壽雄醫師，國立台灣大學醫學院臨床研究所，台北市中山南路 7 號

Pleomorphic Carcinoma of the Lung

Chin-Hung Chang, Jau-Yeong Lu, Shong-Ling Lin*

Objective: To analyze the clinical and pathologic features of biopsy-proven pleomorphic carcinoma of the lung.

Method: We retrospectively reviewed the data of patients with pleomorphic carcinoma of the lung, at a hospital in southern Taiwan. The computerized medical records database of Kaohsiung Veterans General Hospital (VGH-KS) was searched for patients who had pathological findings of pleomorphic carcinoma of the lung from 1999 through 2003. All of the medical records were reviewed, and a microscopic examination of the pathological specimens was performed once again.

Results: Of the 10 patients with histologically confirmed pleomorphic carcinoma, 7 were men and 3 were women, and the median age was 69 years. Initial presenting symptoms were cough (n=10), fatigue (n=8), hemoptysis (n=5), chest wall pain (n=4), weight loss (n=4), dyspnea (n=4) and fever (n=1). The mean size of the tumors was 7.5 cm. The pathological specimens were obtained by transthoracic sono-guided biopsy, CT-guided biopsy or lobectomy during operation. Microscopically, the tumors of five patients were composed of spindle and giant cells exclusively, and the others had epithelial components with squamous cell carcinoma (n=3), adenocarcinoma (n=2) and large cell carcinoma (n=1). Six patients had immunohistochemical staining for their specimens. All of these specimens showed a positive result for cytokeratin stain. The average survival was 6 months.

Conclusions: In our limited experience, the management of pleomorphic carcinoma is not different from that of other non-small cell lung carcinomas (NSCLC). But the histological findings are quite different. Sometimes pleomorphic carcinoma is regarded as sarcoma if there are no carcinomatous transition areas. The most common histological type among our cases was a tumor composed exclusively of spindle and giant cells. ***(Thorac Med 2004; 19: 92-98)***

Key words: pleomorphic carcinoma, giant cell carcinoma, spindle cell carcinoma

Introduction

The recent WHO classification of lung tumors unified the heterogeneous group of non-small cell lung carcinomas (NSCLC), which contain a sarcoma or sarcoma-like component, under the designation "carcinomas with pleomorphic, sarcomatoid or sarcomatous elements" (CPSS) [1,2]. This group includes different entities, such as pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma [1, 2]. The incidence of these tumors in the general

Division of Chest Medicine, Department of Internal Medicine, Department of Pathology and Laboratory Medicine*, KaohsiungVeterans General Hospital
Address reprint requests to: Dr. Jau-Yeong Lu, No. 386, Ta-Chung 1st Rd, Kaohsiung, Taiwan

population is rare, comprising approximately 0.1-0.4% of all lung malignancies [1,2]. These tumors occur predominantly in heavy-smoking males, with an average age of 60 years at diagnosis. The tumors have an aggressive clinical course and commonly appear as biphasic tumors, with a carcinoma (e.g. adenocarcinoma, squamous cell carcinoma, large cell carcinoma or a mixture of these) intermingled with a sarcomatoid (spindle and/or giant cell) component, or with sarcomatous tissue [1-3]. Pleomorphic carcinoma, one subtype of CPSS, is defined as poorly differentiated non-small cell lung cancer containing spindle and/or giant cells, or a carcinoma consisting only of spindle and giant cells [1-4]. The sarcomatoid component, spindle and/or giant cells, must exceed 10% [1-5]. In order to delineate the clinical and pathological features of pleomorphic carcinoma, we reviewed the data of all patients with pleomorphic carcinoma of the lung at VGH-KS from 1999 through 2003. Seven men and 3 women were reviewed. In this report, we describe this rare biphasic-type tumor from the clinical, pathological and radiographic points of view.

Materials and Methods

We retrospectively reviewed the data on pleomorphic carcinoma of the lung at VGH-KS from 1999 through 2003, using the WHO classification of lung cancer proposed in 1999 [5]. The computerized medical records database of VGH-KS was searched for patients who had pathological findings of pleomorphic carcinoma of the lung. All of the medical records were reviewed, and a microscopic examination of the pathological specimens was performed again. The following information was tabulated: (1) age at diagnosis, (2) gender, (3) initial manifestations, (4) tumor size, (5) tumor location, (6) history of tobacco use, (7) microscopic findings, (8) immunohistochemical stain results, (9) type of therapy, and (10) outcome.

Results

Clinical findings (Table 1)

The patient population consisted of 7 men and 3 women between the ages of 44 and 82 years (median, 69). The initial presentation included cough, fatigue, chest wall pain, hemoptysis, weight loss, dyspnea and fever. Six patients had a history of tobacco exposure. Tumor size ranged from 4 to 15 cm (average 7.5 cm). The tumors were predo-

Table 1. Clinical Findings

No	Age at diagnosis	Gender	Initial manifestation history	Smoking (maximal diameter)	Tumor size	Tumor location	Stage
1	56	F	Thoracic pain, cough, fatigue	No	7.5 cm	RUL	Stage IV
2	73	M	Thoracic pain, cough, weight loss, dyspnea, fatigue	Yes	8 cm	RUL	Stage IV
3	70	M	Cough, hemoptysis	Yes	5 cm	RML, RLL	Stage Ib
4	65	M	Thoracic pain, cough, weight loss, fatigue	Yes	5 cm	Right hilum	Stage IV
5	66	M	Cough	Yes	8 cm	RUL	Stage IIIa
6	61	F	Cough, fatigue	No	4.4 cm	LUL	Stage IIIa
7	82	M	Thoracic pain, cough, hemoptysis, weight loss, dyspnea, fatigue, fever	Yes	10 cm	RUL	Stage IIIb
8	78	M	Cough, hemoptysis, weight loss, fatigue	No	7.6 cm	Right hilum	Stage IIb
9	69	M	Cough, hemoptysis, dyspnea, fatigue	Yes	15 cm	RLL	Stage IIIb
10	44	F	Cough, hemoptysis, dyspnea, fatigue	No	4 cm	RLL	Stage IIIa

Table 2. Microscopic Findings

No	Microscopic finding	Immunohistochemical stain
1	Spindle and giant cells	Positive for cytokeratin
2	Spindle and giant cells	Positive for cytokeratin
3	Spindle cells and poorly differentiated SCC	Nil
4	Spindle and giant cells	Positive for cytokeratin and vimentin
5	Spindle, giant cells and poorly differentiated SCC	Nil
6	Spindle cell, adenocarcinoma and SCC	Nil
7	Spindle and giant cells	Positive for cytokeratin, negative for vimentin
8	Spindle, giant and large cells	Positive for cytokeratin, negative for mucin
9	Spindle and giant cells	Positive for cytokeratin, negative for vimentin, CEA
10	Spindle, giant cells and adenocarcinoma	Nil

minantly located in the right lung (9:1), and were located peripherally in 8 patients. At the time of diagnosis, three patients had stage IV disease, two had stage IIIb, three stage IIIa, one stage IIb and one stage Ib.

Microscopic findings (Table 2)

The tumors in five patients were composed exclusively of spindle and giant cells (Figure 1). The shape of the spindle cells was fascicular, whereas the shape of the giant cells was varied, and included polygonal, multiple nuclear and oval types. Five patients had epithelial components, either squamous cell carcinoma (n=3), adenocarcinoma (n=2) or large cell carcinoma (n=1) (Figure 2). Specimens from six patients underwent immunohistochemical staining, and all showed positive results for cytokeratin stain (Figure 3).

Follow-up and outcome (Table 3)

Seven patients had expired as of Nov 2003. Survival ranged from 3 to 19 months, with a mean of 6 months. Among these 7 patients, one with stage IIIa disease received an operation and adjuvant chemotherapy, and survived for 19 months. The patients who were still alive as of Nov 2003, with stage Ib, IIIa or IIIa disease underwent an operation. Both stage IIIa patients received adjuvant chemotherapy post-operation. In our series, four patients received an operation and they seemed to gain an advantage in survival from this.

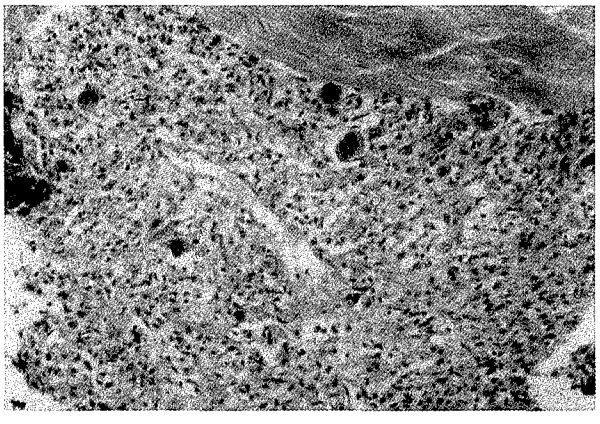

Fig. 1. Pleomorphic carcinoma composed exclusively of spindle and giant cells.

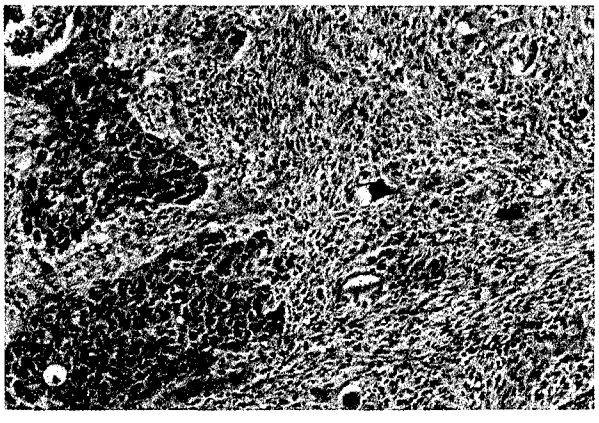

Fig. 2. Pleomorphic carcinoma composed of spindle cells and poorly differentiated squamous cell carcinoma.

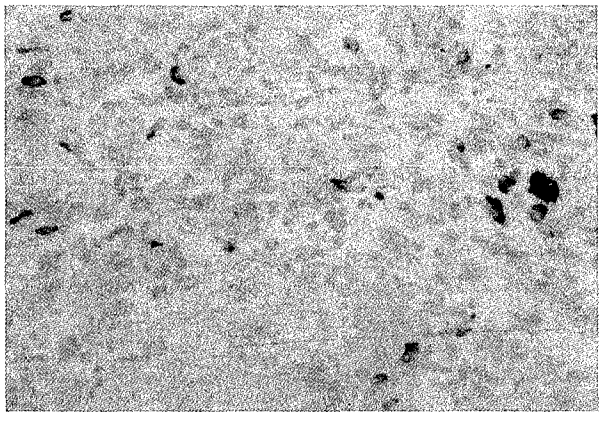

Fig. 3. Pleomorphic carcinoma with positive cytokeratin stain.

Discussion

According to the recent WHO classification of lung tumors, pleomorphic carcinoma of the lung is defined as a poorly differentiated NSCLC containing spindle cells and/or giant cells, or a carcinoma consisting only of spindle and giant cells [5]. According to a previous work by Fishback et al. [3] and to the 1999 WHO classification [5], the pleomorphic carcinoma should comprise at least 10% of spindle and / or giant cells. If a component of small cell carcinoma is found, the tumor is classified as a combined small cell carcinoma [5]. By this definition, we found 10 patients with pleomorphic carcinoma from 1999 through 2003. This tumor shows a fascicular to a single, large or multiple nuclear pattern comprised of atypical spindle and giant cells, and is difficult to distinguish from a true sarcoma, such as malignant fibrous histiocytoma (MFH) and fibrosarcoma, if no carcinomatous areas are found on the hematoxylin and eosin (H&E) sections [6-8]. However, an immunohistochemical stain may help in the differentiation, if the epithelial markers, such as cytokeratin, CEA, EMA or Ber-EP4 are positive [3,10]. With regard to the origin of the neoplastic spindle and giant cells, three hypotheses have been considered. First, carcinoma cells change into neoplastic spindle and giant cells, and remain carcinomatous. Second, these cells originate from carcinoma, but undergo mesenchymal differentiation and change into true sarcoma. Third, these cells originate from sarcoma and differentiate into carcinoma. Since transition carcinomatous areas, immunoreactive for epithelial markers and intracytoplasmic mucin production, are detectable in this kind of tumor, the first hypothesis is plausible [6]. In our series, fifty percent of the tumors were composed exclusively of spindle and giant cells compared with 38.5% in Fishback's series [3].

Pleomorphic carcinoma tends to be a large peripheral lung tumor [3]. The average size of the tumors in our series was 7.5 cm. The tumors of 8 patients were located peripherally. Two patients presented with right shoulder pain due to a Pancoast

Table 3. Follow-up and Outcome (as of Nov 2003)

No	Type of therapy	Stage	Survival length
1	Radiotherapy to tumor	Stage IV	5 months
2	Supportive care	Stage IV	3 months
3	Surgery	Stage Ib	Still alive (> 2 years)
4	Palliative radiotherapy to bone	Stage IV	4 months
5	Surgery + C/T* (CIS + GEM)$^{+}$ x IV	Stage IIIa	Still alive (> 3years)
6	Surgery + C/T (CIS + GEM) x IV	Stage IIIa	Still alive (> 1year)
7	Supportive care	Stage IIIb	4 months
8	Radiotherapy to tumor	Stage IIb	3 months
9	C/T(cyclophosphamide, epirubicin, cisplatin) x II	Stage IIIb	5 months
10	Surgery + C/T (GEM + CIS) x IV	Stage IIIa	19 months

* C/T: Chemotherapy

$^{+}$ CIS : Cisplatin, GEM: Gemcitabine

tumor. Radiotherapy was performed for one patient, and her symptoms improved. The median survival of patients with pleomorphic carcinoma was 10 months in the Fishback et al. series [3], compared with that of ordinary lung carcinomas (20 months for adenocarcinoma, 18.5 months for squamous cell carcinoma, and 12.6 months for large cell carcinoma [16]) and primary sarcoma of the lung (24 months [11] to 28 months [12]). Fishback et al. also reported that pleomorphic carcinomas, with a size > 5 cm, clinical stage > I, and lymph node involvement, shortened patient survival. Due to the limited number of patients, we could not reach the same conclusion. But we found that a patient had a better prognosis if he or she had a resectable tumor. Of 7 mortalities, only one patient had a resectable tumor and received an operation. That patient survived 19 months compared with 3-5 months for those who received supportive care or chemotherapy alone. The prognosis of patients with pleomorphic carcinoma is poor despite surgery, irradiation, and chemotherapy [13]. Some have reported that distant metastases occurred in patients with pleomorphic carcinoma more frequently, earlier and were more closely associated with esophagointestinal metastases [14]. The average postoperative survival was 5 months, while the average post-chemoradiotherapy survival was 2.7 months in one series [15]. However, our patients with resectable tumors had a better prognosis and longer survival.

In conclusion, we have reviewed the clinical, histologic and immunohistochemical findings of 10 cases with pleomorphic carcinoma of the lung. Since this kind of tumor is composed of sarcomatoid cells, it sometimes may be confused with a true sarcoma, if no carcinomatous components are found. Staging in pleomorphic carcinoma plays an important role in the prognosis, and is decisive in whether an operation is suitable. Surgical treatment played an important role in one patient's prognosis in this series. In our experience, however, the management of pleomorphic carcinoma is not different from that of other non-small cell lung cancers.

References

1. Rossi G, Cavazza A, Sturm N, *et al.* Pulmonary carcinoma with pleomorphic, sarcomatoid or sarcomatous elements. Am J Surg Pathol 2003; 27: 311-324.
2. Brambilla E, Travis WD, Colby TV, *et al.* The new World Health Organization classification of lung tumors. Eur Respir J 2001; 18: 1059-68.
3. Fishback NF, Travis WD, Moran CA, *et al.* Pleomorphic (spindle/giant cell) carcinoma of the lung: a clinicopathologic correlation of 78 cases. Cancer 1994; 73: 2936-45.
4. Travis WD. Pathology of lung cancer. Clin Chest Med 2002; 23: 65-8.
5. Travis WD, Colby TV, Corrin B, *et al.* In collaboration with L.H. Sobin and pathologists from 14 countries. World Health Organization International Histological Classification of Tumors. Histological Typing of Lung and Pleural Tumors, 3rd ed. Berlin: Springer-Verlag, 1999; 42-5.
6. Masayoshi Nakajima, Takahiko Kasai, Hiroshi Hashimoto, *et al.* Sarcomatoid carcinoma of the lung–a clinicopathologic study of 37 cases. Cancer 1999; 86: 608-16.
7. Halyard MY, Camoriano JK, Clligan JA, *et al.* Malignant fibrous histiocytoma of the lung. Report of four cases and review of the literature. Cancer 1996; 78: 2492-7.
8. McDonnell T, Kyriakos M, Roper C, *et al.* Malignant fibrous histiocytoma of the lung. Cancer 1988; 61: 137-45.
9. Yousem SA, Hochholzer L. Malignant fibrous histiocytoma of the lung. Cancer 1987; 60: 2532-41.
10. Mark R. Wick, Jon H. Ritter, Peter A. Humphrey. Sarcomatoid carcinoma of the lung. A clinicopathologic review. Am J Clin Pathol 1997; 108: 40-53.
11. Janssen JP, Mulder JJS, Wagenaar SS, *et al.* Primary sarcomas of the lung: a clinical study with long-term follow-up. Ann Thorac Surg 1994; 58: 1151-5.
12. Attanoos RL, Appleton MA, Gibbs AR. Primary sarcomas of the lung: a clinicopathological and immunohistochemical study of 14 cases. Histopathology 1996; 29: 29-36.
13. Davis MP, Eagen RT, Weiland LH. Carcinosarcoma of the lung: Mayo Clinic experience and response to chemotherapy. Mayo Clin Proc 1984; 59: 598-603.
14. Eng J, Sabanathan S. Carcinosarcoma of the lung with gastrointestinal metastasis. Case report. Scand J Thor Cardiovasc Surg 1992; 26: 161-2.
15. Yin-Leong Chang, Yung-Chie Lee, Jin-Yuan Shih, *et al.*

Pulmonary pleomorphic (spindle) cell carcinoma: peculiar clinicopathologic manifestations different from ordinary non-small cell carcinoma. Lung Cancer 2001; 34: 91-97.
16. Kayser K, Bulzebruck H, Probst G, *et al.* Retrospective and prospective tumor staging evaluating prognostic factors in operated bronchus carcinoma patients. Cancer 1987; 59: 355-61.

肺部多形細胞癌

張慶宏　盧朝勇　林秀玲*

目的：分析本院5年當中肺部多形細胞癌 (pleomorphic carcinoma)(共10例) 的臨床病理表現。

方法：從高雄榮民總醫院電腦病歷資料中收尋原發於肺部的多形細胞癌，時段是從 1999 至 2003 年。將病人的臨床表現與病理報告逐一分析。

結果：5年當中共有10個病人符合多形細胞癌的定義。其中7個是男性，3個女性。起始症狀跟一般肺癌類似，但腫瘤平均大小較大 (7.5 公分) 且多位於週邊。5個病人組織學形態上完全是梭狀 (spindle cell) 及巨大 (giant cell) 細胞，另外5個病人的肺癌細胞是由類肉瘤細胞 (sarcomatoid cell) 加上其他非小細胞癌組成。目前3位病人還存活著且均有接受手術治療。死亡的7位病人平均存活時間是6個月。

結論：多形細胞癌處理上跟一般非小細胞癌相似，但是組織學形態卻類似肉瘤 (sarcoma) 。如果切片上沒有其它非小細胞癌區域，有時跟真正肉瘤很難區分，必須借助特殊染色。***(胸腔醫學 2004; 19: 92-98)***

關鍵詞：多形細胞癌，巨大細胞癌，梭狀細胞癌

高雄榮民總醫院　內科部　胸腔內科　病理部 *
索取抽印本請聯絡：盧朝勇醫師，高雄榮民總醫院內科部，高雄市左營區大中一路386號

Predicting Value of Abdominal Perfusion Pressure and Plasma Renin Activity in Mechanically Ventilated Patients

Wen-Te Liu, Mei-Chen Yang, Chung-Jen Huang, Horng-Chyuan Lin, Chun-Hua Wang, Han-Pin Kuo

Rationale: Clinical experience and experimental studies suggest that intra-abdominal hypertension and positive end-expiratory pressure (PEEP) ventilation might alter splanchnic hemodynamics to a significantly greater degree. Our study assessed the influences of raising positive end-expiratory pressure (PEEP) on intra-abdominal pressure (IAP) and the renin-angiotensin-aldosterone system in patients admitted to intensive care unit.

Motheds: Twenty-six mechanically ventilated patients with normal hemodynamic status were recruited. Their IAP, mean arterial pressure (MAP), plasma renin activity, and aldosterone level were measured at 0 and 1 hour after the raising current PEEP level. In addition, we assessed intra-abdominal perfusion by simply calculating abdominal perfusion pressure (APP) as MAP minus IAP. The values of the elevated PEEP were 6 or 10 cmH_2O selectively with the intention of avoiding peak airway pressure beyond 35 cmH_2O. All the patients were followed up until the termination of ICU hospitalization and their mortality rates were recorded.

Results: The patients with a higher IAP and lower APP had significantly elevated renin activity ($n = 26$, $r = 0.64$, $p < 0.001$ and $n = 26$, $r = -0.70$, $p < 0.0001$, respectively). The seven patients who expired in the ICU had significantly elevated renin activity and aldosterone levels and lower APP, compared with the 19 patients who survived ICU hospitalization. Elevated PEEP could significantly affect IAP from 7.9 ± 0.7 to 9.6 ± 0.7 mm Hg ($n = 26$, $p < 0.0001$) and APP from 66.7 ± 1.3 to 65.2 ± 1.4 mm Hg ($n = 26$, $p < 0.05$) respectively. However, there was no significant difference in plasma renin activity and aldosterone levels in the two levels of PEEP. Conclusions Plasma renin activity was significantly correlated with IAP and in an inverse manner, with APP. Higher APP and lower plasma renin revealed better patient outcome. Both IAP and APP were significantly affected by raising the PEEP level. Assessment of APP and plasma renin activity in patients receiving mechanical ventilation can help clinicians in adjusting the ventilator and predict patients' outcome. ***(Thorac Med 2004; 19: 99-108)***

Key words: positive end-expiratory pressure (PEEP), intra-abdominal pressure, abdominal perfusion pressure, plasma renin activity

Department of Thoracic Medicine II, Chang Gung Memorial Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Han-Pin Kuo, Department of Thoracic Medicine II, Chang Gung Memorial Hospital, 199 Tun Hwa N Rd., Taipei, Taiwan

Introduction

Acute elevation of intra-abdominal pressure (IAP) has been shown to adversely affect the cardiac, gastrointestinal, hepatobiliary, pulmonary, and central nervous systems, and renal function [1-5]. Most of the published data describing intra-abdominal hypertension (IAH) were obtained from the observation of surgical patients or through experimental studies.

Elevated IAP influences the respiratory system mechanics through an elevation of the diaphragm, which causes a reduction in respiratory compliance, increased airway pressure, and hypoventilation [6]. Therefore, it is also supposed that in medical patients, especially those who receive mechanical ventilation, a prolonged elevation of IAP may occur during medical intensive care unit (ICU) hospitalization, thus leading to further respiratory distress and subsequently multiple organ dysfunction and eventual death [7]. Animal studies have demonstrated that mechanical ventilation at a high volume and pressure can be deleterious to the lungs [8]. Hyperinflation with intrinsic positive end-expiratory pressure (PEEPi) loads the respiratory muscles and causes dyspnea in obstructive lung disease [9]. Furthermore, the application of PEEP at values greater than PEEPi may substantially aggravate lung hyperinflation, and increase lung volume and peak airway pressure [10]. It is well known that pressure changes during respiration are transmitted to other structures in the mediastinum and abdomen [11]. However, little is known about whether the application of positive pressure ventilation, especially a higher PEEP, with ICU patients will influence their outcome through an effect on the IAP.

The abdominal consequences of an elevated IAP include a reduction in splanchnic and hepatic blood flow and an increase in renal venous pressure [12] with renal blood flow redistribution and oliguria. Therefore, prolonged increased IAP and reduced renal perfusion may also alter the renin-angiotensin system with elevated plasma renin activity and aldosterone levels. The activation of the renin-angiotensin system will aggravate heart failure, arterial hypertension, and electrolyte imbalance [13], as well as enhance susceptibility to T cell-mediated injury in anti-glomerular basement membrane Ab-induced GN [14], thus leading to a poor prognosis critically ill patients.

Cheatham et al [15] suggested that it is unlikely that a single threshold value of IAP can be globally applied to make decisions for all critically ill patients because critical IAP clearly varies from patient to patient and even within the same patient as severity of illness changes. Therefore, a new concept of abdominal perfusion pressure (APP), defined as mean arterial pressure (MAP) minus IAP, was introduced as a superior predictor of outcome in patients with IAH [15].

It is difficult to accurately predict the IAP of patients by clinical assessment alone [16]. Therefore, several new methods have been developed to evaluate intra-abdominal microcirculation directly [17-19]. However, the measurement of intravesicular pressure is still the most simple and effective method [18,20,21]. Therefore, the present study measuring of intravesicular pressure, as well as the effect of raising positive end-expiratory pressure (PEEP) on the change in IAP, to indirectly evaluatethe IAP of mechanically ventilated patients. We also measured plasma renin activity and aldosterone levels in these patients, and estimated their relationships to IAP, APP, and patient outcome.

Materials and Methods

Study Design

This prospective, observational study was designed to assess the effects of artificially increased PEEP on intra-abdominal pressure (IAP) in mechanically ventilated patients.

Patients

Selected respiratory failure victims admitted to the medical intensive care unit of Chang Gung Memorial Hospital between May and November 2002 were enrolled in the study. The eligibility requirements included having undergone endotracheal intubation with mechanical ventilation. None of the

patients had a history of heart failure, intra-abdominal, prostate, or bladder surgery. All had a Foley catheter inserted into the urinary bladder. The hemodynamic status was stable, with mean arterial pressure (MAP) ≥ 70 mm Hg. During the study period, the patient's peak airway pres-sure was kept ≤ 35 cm H_2O with no inotropic agent prescribed.

Intra-abdominal pressure measuring

Urinary bladder pressure measurement as an estimation of IAP is simple, reliable, and widely accepted [22]. Each patient, with a 14-French Foley catheter inserted was placed in the supine position and kept flat for recordings. We connected the Foley catheter to a device designed for measuring central venous pressure ("C.V.P. scale system", SIGMA®). After draining the bladder and clamping the distal part of the catheter from the connecting site, 60 mL of water was infused. The tubing of the C.V.P. scale system was carefully examined to avoid kinks and air bubbles. The bladder pressure was assessed as the height of the column of fluid measured from the meniscus to the anterior iliac crest. The column of fluid was observed for appropriate respiratory variation, and all measurements were taken at end-expiration.

Study protocol

The baseline data, including mean arterial pres-sure, intra-abdominal pressure, ventilator pres-sure (positive end-expiratory pressure, peak inspir-atory pressure), plasma renin activity and aldos-terone level were collected initially. We took these patients' blood samples between 9 a.m. and 10 a.m. to avoid circadian differences in renin and aldosterone. Then we selectively raised the PEEP level 6 or 10 cmH_2O above the current value to avoid a peak airway pressure beyond 35 cmH_2O. All measurement that were done before were taken again 60 minutes later, then the PEEP level was reverted to the previous value. We also recorded the APP at the two levels of PEEP by calculating MAP minus IAP. All patients were followed up until the termination of ICU hospitalization. They were divided into two groups based on survival or not at ICU discharge. All the parameters described above were compared between these two groups.

Plasma renin and aldosterone assays

The aldosterone concentration was measured from the serum of a 10-ml blood sample (Count-A-Count, D.P.C., Los Angeles, CA, USA). Normal values for seated patients range between 40 and 310 pg/ml. The conversion factor for SAC measured in pg/ml into pmol/l (SI units) is 2.775.

The active renin concentration was determined in plasma using an immunoradiometric assay (IRMA, Active Renin, Nichols®, CA, USA). This method shows a strong correlation with commercial plasma renin activity assay methods (correlation coefficient r = 0.91). The normal range in seated patients is between 4.2 and 45.6 pg/ml. The sensitivity of the assay as deter-mined by the 95% confidence interval of 20 repli-cates of the Zero Standard is 0.84 pg/ml. The intra-assay variation is 2.5% and the interassay variation 7.96%.

Statistical analysis

All measured data in the two levels of PEEP ventilation were compared through a paired t-test. If scatter plots suggested deviations from normality, a nonparametric analysis (Wilcoxon matched paired test) was used. Change from baseline was expressed as mean±SE. Linear regressions using plasma renin activity and aldosterone levels as the dependent variables and IAP, APP, and MAP as independent variables were performed to quantify the relationship between these variables. We calculated an unpaired two-tailed t-test to differentiate the survival and mortality groups during ICU hospitalization. Statistical significance was assumed at $p < 0.05$.

Results

Twenty-six mechanically ventilated patients were entered into the study. The patients' demographic data are listed in Table 1. Plasma renin activity (n=26) was significantly correlated to the level of basal IAP ($r = 0.64$, $p < 0.001$), and inversely correlated to the level of basal APP ($r = -0.70$, $p <$

0.0001). There was also a significantly inverse correlation between MAP and plasma renin activity ($r = -0.50$, $p < 0.05$). However, the levels of basal IAP, APP and MAP didn't significantly correlate to the plasma aldosterone level (Figure 1).

We assessed the patient outcome based on the presence of ICU mortality. Seven patients expired during their ICU stay; the remainding patients (19 patients) were successfully extubated and then transferred to the general ward. Compared with those who survived at ICU discharge, these 7 expired patients had significantly lower APP (62.1±2.4 vs. 68.5±1.4 mmHg) and higher levels of plasma renin activity and aldosterone (138.8±54.3 vs. 43.0±8.8 ng/ml/hr. and 153.2±50.7 vs. 58.0±7.7 ng/dl, respectively) (Table 2).

The changes in IAP occurred immediately after elevating the PEEP level and persisted until the PEEP was reverted to its previous value. At a high PEEP level, the IAP of 24 patients had increased, one decreased and one had no change. Raising the PEEP generated a significant increase in IAP from 7.9±0.7 to 9.6±0.7 mm Hg ($n = 26$, $p < 0.0001$) and a significant decrease in APP from 66.7±1.3 to

Table 1. General demographic data from the study population (n = 26)

Patient No.	Age (yrs)	Main Diagnosis	Sex	PEEP Basal – higher	Ppeak Basal - higher	ICU mortality
1	82	Pneumonia	M	8 – 18	17 – 27	-
2	76	Pneumonia	M	6 – 16	13 – 23	-
3	74	Right empyema,	M	10 – 16	28 – 35	-
4	76	Urosepsis	F	8 – 14	28 – 34	Y
5	69	COPD	M	6 – 16	18 – 25	-
6	69	Pneumonia	M	6 – 16	17 – 28	-
7	85	Pneumonia	M	8 – 14	24 – 30	Y
8	75	Acute on CRF	F	6 – 16	15 – 25	-
9	81	Pneumonia	M	6 – 12	27 – 33	Y
10	81	Pneumonia	M	8 – 18	25 – 34	-
11	72	Bronchiectasis	F	6 – 12	25 – 31	Y
12	85	Bronchiectasis	M	8 – 14	24 – 30	-
13	75	Urosepsis	F	6 – 12	23 – 30	Y
14	82	Urosepsis	F	6 – 12	24 – 31	Y
15	78	COPD	M	8 – 14	25 – 33	-
16	69	Pneumonia	F	8 – 14	18 – 24	-
17	76	COPD	M	10 – 16	23 – 30	-
18	81	Pneumonia	M	12 – 18	26 – 33	-
19	72	Pneumonia	M	6 – 16	21 – 28	-
20	69	Pneumnia	F	6 – 16	22 – 28	-
21	54	Organophosphate intoxication	M	8 – 14	24 – 30	-
22	67	Pneumonia	F	8 – 14	23 – 30	-
23	73	Pneumonia	M	10 – 16	24 – 30	-
24	66	COPD	M	8 – 18	22 – 31	-
25	73	Pneumonia	F	6 – 16	18 – 28	-
26	72	Pneumonia	F	6 – 16	21 – 30	Y

Ppeak, peak inspiratory pressure, cm H_2O; PEEP, positive end-expiratory pressure, cm H_2O; CRF, chronic renal failure.

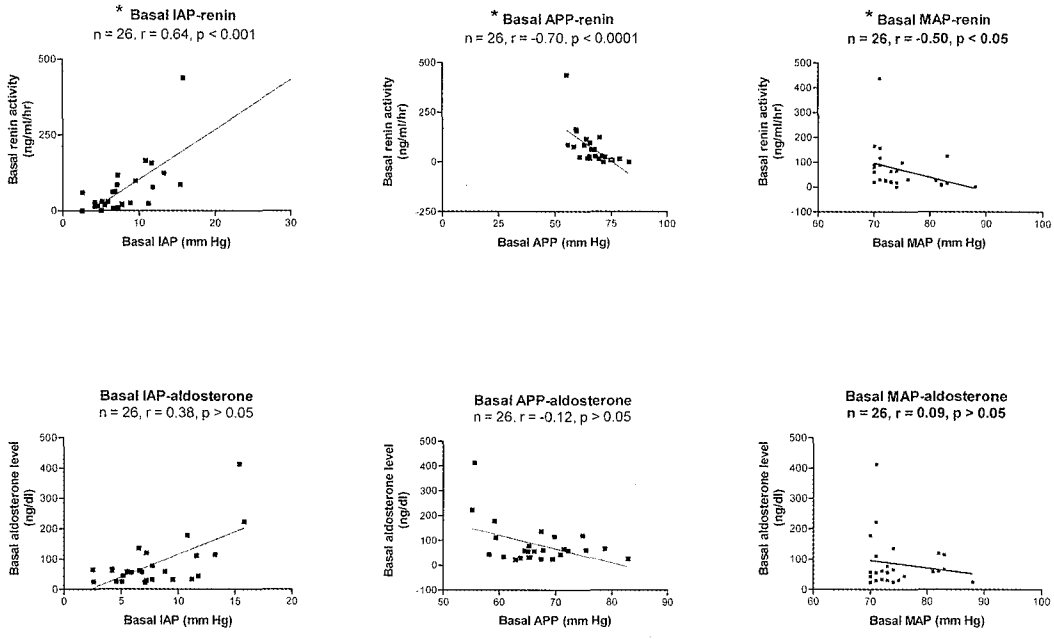

Fig. 1. Correlations between intra-abdominal pressure (IAP), abdominal perfusion pressure (APP), mean arterial pressure (MAP) and plasma renin activity, aldosterone level at basal-PEEP level. *Spearman correlation, $p < .05$

Table 2. Comparison of APP, MAP, IAP, plasma renin activity and aldosterone level between patients with and without ICU mortality (basal PEEP level)

ICU mortality	APP mm Hg	MAP mm Hg	IAP mm Hg	Renin ng/ml/hr	Aldosterone ng/dl
Yes, n = 7	62.1 ± 2.4	71.4 ± 0.6	9.4 ± 2.1	138.8 ± 54.3	153.2 ± 50.7
No, n = 19	68.5 ± 1.4	75.8 ± 1.3	7.3 ± 0.6	43.0 ± 8.8	58.0 ± 7.7
P value	< 0.05	NS	NS	< 0.05	< 0.01

Unpaired t test, $p > 0.05$: NS, no significance

65.2±1.4 mm Hg (n = 26, p < 0.01). However, elevated PEEP didn't affect MAP (from 74.6±1.0 to 74.8±1.0 mmHg), plasma renin activity (from 68.8±17.4 to 70.2±17.7 ng/ml/hr), or the aldosterone level (from 83.7±16.4 to 93.2±16.6 ng/dl) significantly (Figure 2).

Discussion

In the present study, the patients with a higher IAP had elevated plasma renin activity. Raising the PEEP level in mechanically ventilated patients will significantly increase their IAP. All of the results described above are discussed herein for their clinical implications and further application:

Elevated IAP versus plasma renin activity and aldosterone level

Previous experimental studies and clinical observation have demonstrated that acute elevated IAP affects intra-abdominal organ perfusion with a manifestation of increased plasma renin activity and aldosterone levels [1,3,4,22,23]. In our patients, the higher the IAP, the higher the measured plasma renin activity, suggesting that IAP may regulate the renin-angiotensin-system through a direct effect on renal perfusion [24-26]. However, the direct measurement of intra-abdominal organ perfusion requires more invasive, time-consuming and expensive intervention [19]. Cheatham et al [15] proposed the concept that a simple calculation of abdominal

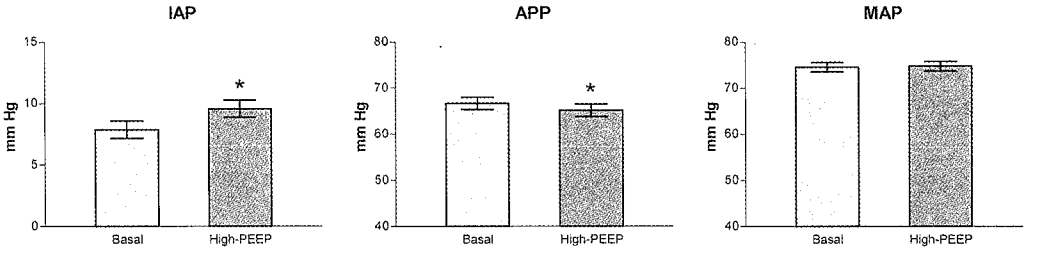

Fig. 2. Effect of the elevated positive end-expiratory pressure (PEEP) on intra-abdominal pressure (IAP), mean arterial pressure (MAP), abdominal perfusion pressure (APP). *Wilcoxon signed rank test, $p < .05$

perfusion pressure (APP), defined as mean arterial pressure (MAP) minus IAP, should be a superior parameter to either MAP or IAP alone in the assessment of intra-abdominal hypertension. In the present study, IAP, APP and MAP were significantly correlated to plasma renin activity and APP seemed to be the most linearly related among the three parameters. Although the concept of simply calculating APP as MAP minus IAP requires further prospective studies [15], the most significant correlation between APP and plasma renin activity is consistent with the theory that all the major factors regulating renin secretion are related to effective intravascular volume, i.e. intra-abdominal organ perfusion [27-29]. On the other hand, the plasma aldosterone level was not related to APP and MAP. Angiotensin II and an elevated plasma potassium concentration are the major stimuli of aldosterone secretion which can also be enhanced by adrenocorticotropic hormone (ACTH) and hyponatremia, but suppressed by atrial natriuretic peptide [30-32]. Among these factors, the production of angiotensin II and atrial natriuretic peptide varies with volume status which affects aldosterone and renin in the same manner. However, the ACTH level, plasma potassium and sodium concentration may have varied between our patients. This explains the discrepancy between plasma renin activity and the aldosterone level in the present study. In addition, there are extrarenal renin-angiotensin systems that can synthesize angiotensin II at a variety of sites, including the kidney, vascular endothelium, adrenal gland, and brain [33,34]. It is the local effect of the renin-angiotensin system that can play an important role in the regulation of vascular tone and possibly in the development of hypertension. However, these local effects cannot release enough renin or angiotensin II into systemic circulation, so measurement of the plasma renin activity or angiotensin II levels may be a misleading estimate of the tissue activity in this system [35,36]. Moreover, Findling et al [37] also observed that a significant subset (21%) of seriously ill patients have inappropriately low aldosterone levels, despite elevated plasma renin activity. This dissociation is not due to an impairment of angiotensin II production or changes in plasma ACTH or K+. This phenomenon is associated with a higher mortality during critical illness. In light of the evidence of decreased adrenal androgen secretion during severe illness, this dissociation of renin and aldosterone may represent an additional adrenal adaptation designed to promote cortisol production in critically ill patients [37]. This result may explain why APP seemed to be more linearly related with renin activity than aldosterone and why there exists an inconsistency between renin and aldosterone in our study.

In addition, the methods used to measure renin and aldosterone may influence the results. We took the blood samples between 9 a.m. and 10 a.m. to avoid the circadian differences. However, there were some shortcomings to this procedure. First, the effect of tourniquet related blood stasis may have lowered renin levels markedly. Second, the measurement of plasma renin concentration provides considerable advantages over the more widely measured plasma renin activity. Plasma renin activity means the rate of angiotensin I formation per

unit of time. However, renin substrate (on which renin acts) is normally not present in sufficient quantities for maximal renin effect. In the method used to check plasma renin concentration, excess renin substrate is added to measure the maximal renin effect, then the result is compared with standard renin preparations to calculate the patient's renin concentration. Measuring plasma renin activity is adequate for clinical purposes and is technically a little easier. Estrogens increase renin substrate, so the plasma renin concentration would be more accurate in that situation [42].

The importance of AAP in the prediction of outcome

Cheatham et al [15] suggested that IAP measurements alone do not have sufficient sensitivity and specificity to be useful as a resuscitation endpoint or predictor of mortality in patients with IAH. The abdominal perfusion gradient or APP seems to be the best predictor of patient outcome when compared with MAP, IAP, or other traditional resuscitation endpoints, such as arterial pH, base deficit, arterial lactate, and hourly urinary output. Many of these parameters are maintained at relatively normal levels until late in the progression of IAH, at which point end organ dysfunction is imminent and progression to ACS is inevitable. However, the calculation of APP addresses not only the severity of IAH present at that time, but also the adequacy of tissue perfusion and the need for additional resuscitation. Our data, consistent with that of a previous study [15], reveal that a lower level of APP foretells a better prognosis, suggesting routine measurement of APP levels in critical ill patients is worthwhile.

Patient outcome

Previous studies revealed that patients who suffer abdominal trauma or receive abdominal surgical intervention may develop intra-abdominal hypertension which causes further morbidity and mortality [7,40,41]. Although patients' IAP is this study was relatively lower than that in patients who undergo surgery or suffer abdominal trauma, there was also a significant difference in APP, and in the renin and aldosterone levels between the patients that expired or survived to ICU discharge, indicating that even in the ICU, prolonged elevated IAP (i.e., persistently low APP) may have a significant influence on patient outcome [15]. Our results also show that in these normotensive patients, the renin and aldosterone levels differed markedly between who expired in the ICU and those who surived, suggesting that in critical ill patients with normal blood pressure, lower APP combined with higher renin or aldosterone levels may indicate a poor intra-abdominal perfusion and outcome.

Effects of raising positive end-expiratory pressure

Positive end-expiratory pressure (PEEP) ventilation and intra-abdominal hypertension can cumulatively deteriorate visceral perfusion [24,38]. Our study revealed the significant effects of raising PEEP on IAP and APP. However, there was no significant difference in MAP, renin activity and the aldosterone level between the two levels of PEEP. We believe that the change in plasma renin activity and aldosterone level is time-consuming and that the one hour application of PEEP in our study was too short a duration to raise their level [39]. Further long-term observation of the time course needed to change renin and aldosterone concentrations at different levels of IAP is required.

Conclusion

Our study revealed that intra-abdominal pressure was significantly correlated with plasma renin activity. Abdominal perfusion pressure, the newly proposed concept MAP minus IAP, was also correlated with the level of plasma renin and was a better predictor of intra-abdominal perfusion and patient outcome than IAP itself. Furthermore, raising the PEEP level increased IAP and APP significantly. In many situations, most patients receiving mechanical ventilation in the ICU may need a high PEEP level. We concluded that the assessment of APP and plasma renin activity can help us to evaluate the optimal PEEP level and predict patient outcome.

References

1. Gudmundsson FF, Gislason HG, Myking OL, *et al.* Hormonal changes related to reduced renal blood flow and low urine output under prolonged increased intra-abdominal pressure in pigs. Eur J Surg. 2002; 168(3): 178-86.
2. Yavuz Y, Ronning K, Lyng O, *et al.* Effect of increased intraabdominal pressure on cardiac output and tissue blood flow assessed by color-labeled microspheres in the pig. Surg Endosc. 2001; 15(2): 149-55.
3. Sugerman HJ. Effects of increased intra-abdominal pressure in severe obesity. Surg Clin North Am. 2001; 81(5): 1063-75, vi.
4. Altintas F, Tunali Y, Bozkurt P, *et al.* An experimental study on the relationship of intra-abdominal pressure and renal ischemia. Middle East J Anesthesiol. 2001; 16(1): 55-66.
5. Citerio G, Vascotto E, Villa F, *et al.* Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. Crit Care Med. 2001; 29(7): 1466-71.
6. Schein M, Wittman DH, Aprahamian CC, *et al.* The abdominal compartment syndrome: The physiological and clinical consequences of elevated intra-abdominal pressure. J Am Coll Surg 1995; 180: 745-53.
7. Morken J, West MA. Abdominal compartment syndrome in the intensive care unit. Curr Opin Crit Care. 2001; 7(4): 268-74.
8. Brochard L, Roudot-Thoraval F. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. American Journal of Respiratory & Critical Care Medicine. 158(6): 1831-8, 1998 Dec.
9. Fessler HE, Brower RG, Permutt S. CPAP reduces inspiratory work more than dyspnea during hyperinflation with intrinsic PEEP. Chest. 108(2): 432-40, 1995 Aug.
10. Tan IK, Bhatt SB, Tam YH, *et al.* British Journal of Anaesthesia. 70(3): 267-72, 1993 Mar.
11. Chieveley-Williams S, Dinner L, Puddicombe A, *et al.* Central venous and bladder pressure reflect transdiaphragmatic pressure during pressure support ventilation. Chest. 121(2): 533-8, 2002 Feb.
12. Jacques T, Lee R. Improvement of renal function after relief of raised intra-abdominal pressure due to traumatic retroperitoneal haematoma. Anaesth Intensive Care 1988; 16: 478-82.
13. Zaman MA, Oparil S, Calhoun DA. Drugs targeting the renin-angiotensin-aldosterone system. Nature Reviews. Drug Discovery. 1(8): 621-36, 2002 Aug.
14. Suzuki Y. Susceptibility to T cell-mediated injury in immune complex disease is linked to local activation of renin-angiotensin system: The role of NF-AT pathway. Journal of Immunology. 169(8): 4136-46, 2002 Oct 15.
15. Cheatham ML, White MW, Sagraves SG, *et al.* Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. J Trauma. 2000; 49(4): 621-6; discussion 626-7.
16. Sugrue M, Bauman A, Jones F, *et al.* Clinical examination is an inaccurate predictor of intraabdominal pressure. World J Surg. 2002; 26(12).
17. Samel ST, Neufang T, Mueller A, *et al.* A new abdominal cavity chamber to study the impact of increased intra-abdominal pressure on microcirculation of gut mucosa by using video microscopy in rats. Crit Care Med. 2002; 30 (8): 1854-8.
18. Engum SA, Kogon B, Jensen E, *et al.* Gastric tonometry and direct intraabdominal pressure monitoring in abdominal compartment syndrome. J Pediatr Surg. 2002; 37(2): 214-8.
19. Varela JE, Cohn SM, Giannotti GD, *et al.* Near-infrared spectroscopy reflects changes in mesenteric and systemic perfusion during abdominal compartment syndrome. Surgery. 2001; 129(3): 363-70.
20. Lee SL, Anderson JT, Kraut EJ, *et al.* A simplified approach to the diagnosis of elevated intra-abdominal pressure. J Trauma. 2002; 52(6): 1169-72.
21. Fusco MA, Martin RS, Chang MC. Estimation of intra-abdominal pressure by bladder pressure measurement: validity and methodology. J Trauma. 2001; 50(2): 297-302.
22. Bloomfield GL, Blocher CR, Fakhry IF, *et al.* Elevated intra-abdominal pressure increases plasma renin activity and aldosterone levels. J Trauma. 1997; 42(6): 997-1004; discussion 1004-5.
23. Cabrera J, Falcon L, Gorriz E, *et al.* Abdominal decompression plays a major role in early postparacentesis haemodynamic changes in cirrhotic patients with tense ascites. Gut. 2001; 48(3): 384-9.
24. Kotzampassi K, Paramythiotis D, Eleftheriadis E. Deterioration of visceral perfusion caused by intra-abdominal hypertension in pigs ventilated with positive end-expiratory

pressure. Surg Today. 2000; 30(11): 987-92.
25. Agusti M, Elizalde JI, Adalia R, et al. Dobutamine restores intestinal mucosal blood flow in a porcine model of intra-abdominal hyperpressure. Crit Care Med. 2000; 28(2): 467-72.
26. Bongard F, Pianim N, Dubecz S, *et al.* Adverse consequences of increased intra-abdominal pressure on bowel tissue oxygen. J Trauma. 1995; 39(3): 519-24; discussion 524-5.
27. Bock HA, Hermle M, Brunner FP, *et al.* Pressure dependent modulation of renin release in isolated perfused glomeruli. Kidney Int. 1992; 41(2): 275-80.
28. Kopp U, DiBona GF. Interaction of renal beta 1-adrenoceptors and prostaglandins in reflex renin release. Am J Physiol. 1983; 244(4): F418-24.
29. Lorenz JN, Weihprecht H, Schnermann J, *et al.* Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. Am J Physiol. 1991; 260(4 Pt 2): F486-93.
30. Young DB. Quantitative analysis of aldosterone's role in potassium regulation. Am J Physiol. 1988; 255(5 Pt 2): F811-22.
31. Shibata H, Ogishima T, Mitani F, *et al.* Regulation of aldosterone synthase cytochrome P-450 in rat adrenals by angiotensin II and potassium. Endocrinology. 1991; 128 (5): 2534-9.
32. Adler GK, Chen R, Menachery AI, *et al.* Sodium restriction increases aldosterone biosynthesis by increasing late pathway, but not early pathway, messenger ribonucleic acid levels and enzyme activity in normotensive rats. Endocrinology. 1993; 133(5): 2235-40.
33. Naftilan AJ, Zuo WM, Inglefinger J, *et al.* Localization and differential regulation of angiotensinogen mRNA expression in the vessel wall. J Clin Invest. 1991; 87(4): 1300-11.
34. Wagner C, Jensen BL, Kramer BK, *et al.* Control of the renal renin system by local factors. Kidney Int Suppl. 1998; 67: S78-83.
35. Bader M, Zhao Y, Sander M, *et al.* Role of tissue renin in the pathophysiology of hypertension in TGR(mREN2)27 rats. Hypertension. 1992; 19(6 Pt 2): 681-6.
36. Hilgers KF, Peters J, Veelken R, *et al.* Increased vascular angiotensin formation in female rats harboring the mouse Ren-2 gene. Hypertension. 1992; 19(6 Pt 2): 687-91.
37. Findling JW, Waters VO, Raff H. The dissociation of renin and aldosterone during critical illness. Journal of Clinical Endocrinology & Metabolism. 64(3): 592-5, 1987 Mar.
38. Sugrue M, D'Amours S. The problems with positive end expiratory pressure (PEEP) in association with abdominal compartment syndrome (ACS). J Trauma. 2001; 51(2): 419-20.
39. Bloomfield GL, Sugerman HJ, Blocher CR, *et al.* Chronically increased intra-abdominal pressure produces systemic hypertension in dogs. Int J Obes Relat Metab Disord. 2000; 24(7): 819-24.
40. Hong JJ, Cohn SM, Perez JM, *et al.* Prospective study of the incidence and outcome of intra-abdominal hypertension and the abdominal compartment syndrome. Br J Surg. 2002; 89(5): 591-6.
41. Jakob SM. Clinical review: splanchnic ischaemia. Crit Care. 2002; 6(4): 306-12.
42. Louis St. Chapter 30: Adrenal function tests, Ravel: Clinical Laboratory Medicine, 6th ed, 1995. 514-5.

腹內灌流壓及血清腎激素對於病人使用呼吸器臨床預後的評估價值

劉文德　楊美貞　黃崇仁　林鴻銓　王圳華　郭漢彬

背景：臨床經驗與動物實驗都可以發現：腹腔內的高壓以及維持呼氣末端正壓的呼吸方式(Positive end-expiratory pressure，PEEP)，會對於腹腔內器官的血行動力狀態造成顯著的改變。我們研究增加呼氣末端正壓值對於腹內壓與 renin-angiotensin-aldosterone system 的影響。

方法：總計 26 位氣管插管使用呼吸器且血行動力學穩定的病患被納入這次研究，我們測量這些病患的腹內壓、平均動脈壓、血清腎激素(plasma renin activity)與醛固酮(aldosterone level)的濃度，在其他因素不變的情形下增加 PEEP(6 或 10 cmH_2O，避免最大呼吸道阻力超過 35 cmH_2O)，一小時後再次測量上述的變因；另外並定義腹內灌流壓(abdominal perfusion pressure)為平均動脈壓與腹內壓的差值。這些病患被持續追蹤至離開加護病房並紀錄其死亡率。

結果：在腹內壓較高(higher intra-abdominal pressure)及腹內灌流壓較低(lower abdominal perfusion pressure)的病人身上可以觀察到顯著偏高的血清腎激素。加護病房住院期間死亡的 7 位病患身上可以觀察到顯著較高的血清腎激素(plasma renin activity)與醛固酮(plasma aldosterone level)，他們的腹內灌流壓則明顯低於存活的另外 19 位病患。增加 PEEP 會顯著提高腹內壓與減低腹內灌流壓(abdominal perfusion pressure)。然而，比較 PEEP 提高前後血清腎激素(plasma renin activity)與醛固酮(aldosterone level)的濃度則沒有顯著的差異。

結論：本篇研究發現，腹內壓(Intra-abdominal pressure)及腹內灌流壓(Abdominal perfusion pressure)皆和血清腎激素的多寡呈顯著相關；較高的腹內灌流壓與較低的血清腎激素顯示病人有較好的預後。而腹內壓及腹內灌流壓亦會受到 PEEP 調整的影響，因此測量腹內灌流壓及血清腎激素有助於臨床醫師對重症病人的評估與呼吸器的調整。*(胸腔醫學 2004; 19: 99-108)*

關鍵詞：呼氣末端正壓(PEEP)，腹內壓，腹內灌流壓，血清腎激素

林口長庚紀念醫院　胸腔二科
索取抽印本請聯絡：郭漢彬醫師，林口長庚紀念醫院胸腔二科，桃園縣龜山鄉復興街 5 號

Spontaneous Catheter Migration of Implantable Vascular Access Device — Two Case Reports and Review of the Literature

Chien-Ho Tsai, Han-Shui Hsu, Wei-Juin Su, Hsin-Liang Lai,
Liang-Shun Wang, Min-Hsiung Huang

The implantable vascular access device (IVAD), sometimes called the "implantable infusion port", is usually used for drawing blood samples, administering drugs, and supplying fluids or nutrition. Some of the complications that cause malfunctioning of the device have been reported. We describe herein two unusual cases with a spontaneous catheter migration of the IVAD. In the first case, the initial port malfunctioning was followed by a total occlusion and an inability to infuse. In the second case, the port malfunctioned, and only sometimes was not in a full-running mode during infusion. A migration of the central venous catheter can lead to vascular, neurologic, or infectious complications. Although some authors have reported non-operative methods to correct the positioning of the displaced central venous catheter, it is difficult to re-position the catheter of an IVAD, which is implanted completely subcutaneously. Removal and replacement are usually necessary in these cases. ***(Thorac Med 2004; 19: 109-114)***

Key words: migration, catheter, implantable vascular access device

Introduction

In cancer patients with locally advanced tumors or distant metastases, chemotherapy is the treatment of choice. The administration of chemotherapeutic drugs usually requires an implantable vascular access device (IVAD). The device is usually implanted in the upper chest, and the catheter is inserted into the great vein of the thorax. More than 1,200 cancer patients per year undergo IVAD implantation surgery at our institution. Secondary migration indicates the malpositioning of a catheter that was initially in the proper location. These cases are unusual. We report herein two cases with the spontaneous catheter migration of an IVAD, and review the literature. We discuss the causes, complications and methods of management.

Case Reports

Case 1

A 61-year-old female was a patient with adenocarcinoma of the lung with right malignant pleural effusion and lung-to-lung metastasis; the clinical staging was T4N3M1, stage IV. Since the patient had to receive long-term chemotherapy, she underwent a subcutaneous IVAD implantation via the left cephalic vein. The surgery was performed uneventfully, and the catheter positioning was checked with C-arm fluoroscopy intra-operatively.

Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Han-Shui Hsu, 201, Sec 2, Shih-Pai Road, Taipei, Taiwan 112

The postoperative chest X-ray (Figure 1) showed the tip of the catheter positioned at the junction of the innominate vein and the superior vena cava. She received a course of chemotherapy through this device. Two weeks later, the follow-up chest X-ray film showed that the tip of the catheter had migrated to the ipsilateral internal jugular vein (Figure 2). The device was still functioning well at that time. She was taken to the operating room 6 months after the first surgery. This totally occluded subcutaneous IVAD was removed and a new one was implanted on the right side without difficulty.

Case 2

A 62-year-old male was a victim of adenocarcinoma of the RUL with mediastinal lymphadenopathy, pleural seeding and right-side massive malignant pleural effusion; the clinical staging was T4N2M0, stage IIIB. He required long-term chemotherapy. He underwent a subcutaneous IVAD implantation surgery via the left cephalic vein. The surgery was performed without difficulty, and C-arm fluoroscopy revealed the proper positioning of the catheter tip during operation. The postoperative chest X-ray (Figure 3) showed that the tip of the catheter was at the junction of the innominate vein and the superior vena cava. On a film taken 5 weeks after the previous X-ray, and 2 months after the emplacement of the device, the tip of the catheter was noted to have migrated backward via the left subclavian vein (Figure 4). No management was undertaken at that time. Another film taken 9 days later showed a circular kinking of the catheter (Figure 5). The patient was taken to the operating room, where the device was removed. He refused re-implantation of a new device and further chemotherapy because he could not tolerate the side effects of the treatment.

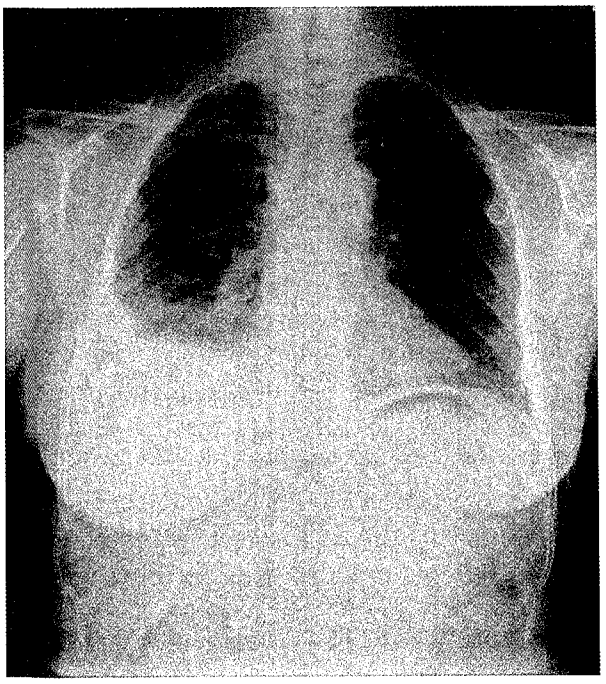

Fig. 1. The tip of the catheter was at the junction of the innominate vein and the superior vena cava.

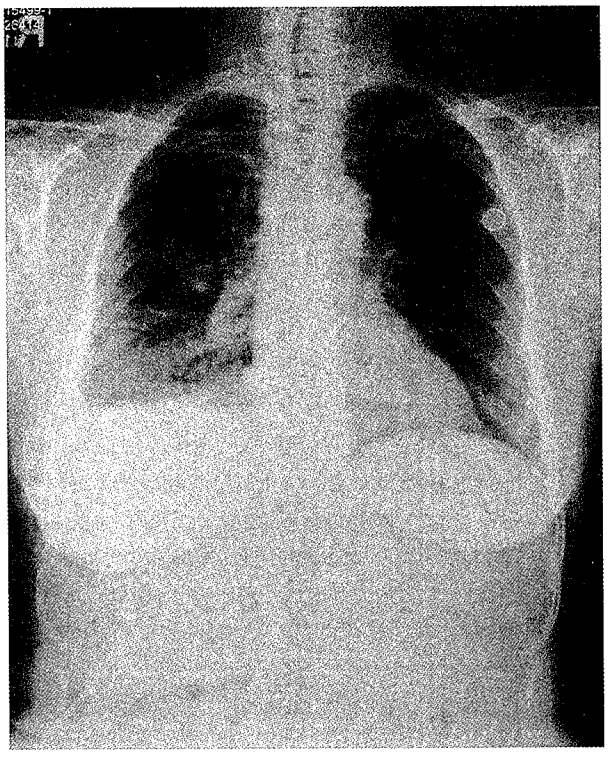

Fig. 2. Follow-up 2 weeks later. Chest X-ray film shows the tip of the catheter has migrated to the ipsilateral internal jugular vein.

Discussion

The totally implanted venous and arterial access system, which replace the use of external catheters in cancer treatment, was introduced in 1982 [1].

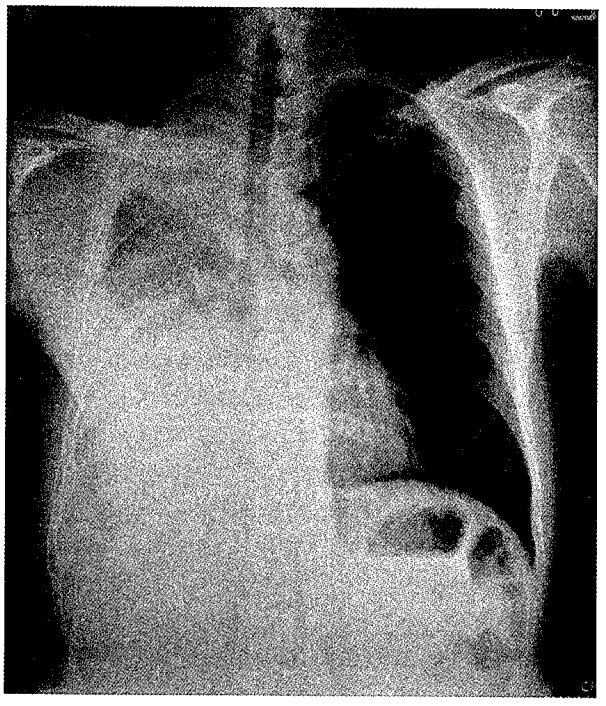

Fig. 3. The tip of the catheter was at the junction of the innominate vein and the superior vena cava.

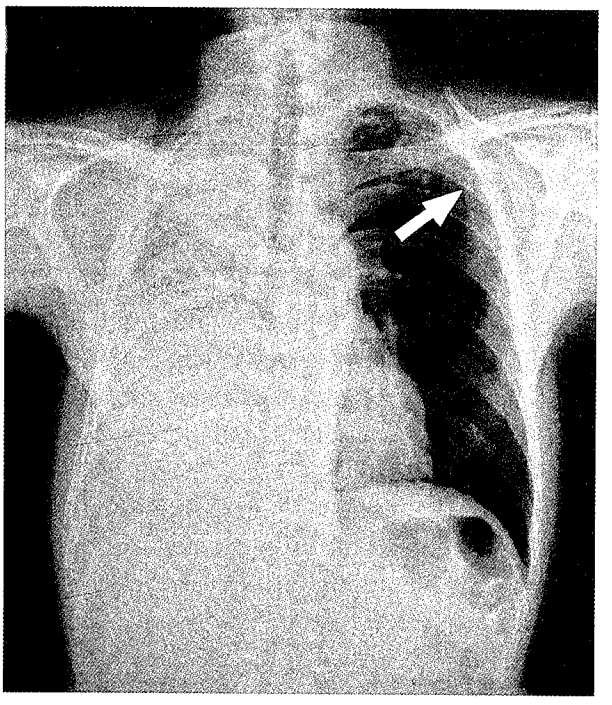

Fig. 4. Five weeks later (2 months after placement of the device), the tip of the catheter has migrated backward via the left subclavian vein. (see arrow)

Along with the increasing use of IVADs has come an expanding variety of complications. Many complications are discovered at the time of operation, others can occur at a later time. Malpositioning of the catheter at the time of operation is easily identified by fluoroscopy, and a re-directioning manipulation can be done immediately, before the wound closes. We describe two cases with a secondary migration of the catheter. In case 1, the patency of the device was gradually compromised because of malpositioning. We re-implanted a new device after the first one had been removed. In case 2, we removed the device to prevent any further undesired migration of the catheter. Some series have reported the spontaneous migration of the central venous catheter. Lum and Soski reported 25 spontaneous migrations among 1794 external central venous catheters emplaced over a 5-month period (2.4%) [2]. Krasnow encountered 4 migrations of 60 Hickman catheters (6.7%) in a period of 4 days to 3 weeks after emplacement [3]. In our study, the catheter migrated within 2 weeks in case 1, and in

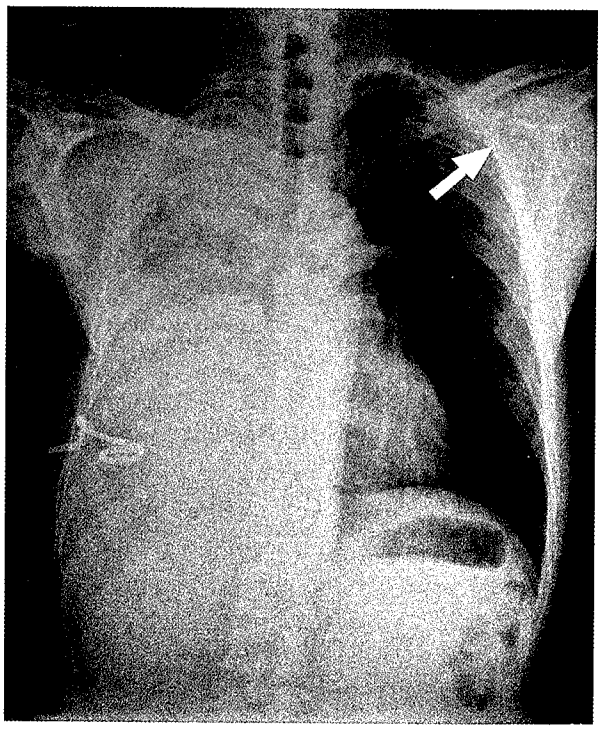

Fig. 5. Intravascular circular kinking of the catheter. (see arrow)

case 2, it migrated spontaneously 2 months after implantation.

In the first case presented herein, the catheter, which had migrated into the wrong position, was not removed immediately, because it was still functioning fairly well when the improper positioning was recognized. Vazquez encountered a spontaneous re-directing to the proper position of a previously malpositioned catheter, without any manipulation [4]. However, the potential risk of infection due to a malpositioned catheter has been reported [5]. The spontaneous migration of catheters will also lead to the potentially harmful side effects of drugs or hypertonic solution injected into the smaller peripheral veins, and local phlebitis or venous thrombosis could occur. Infusion of hypertonic solutions into the internal jugular vein has been reported to cause cortical venous thrombosis of the brain [6]. When retrograde infusion is given, venous return is retarded by increasing of the static venous pressure. In our experience, we found facial edema in another patient during infusion via a malpositioned external central venous catheter with the tip misplaced distally into the internal jugular vein. Other complications include neck, shoulder, or ear pain, or neurologic deficits. The central venous catheter may remain for a time in the wrong position before it is recognized. Some authors have suggested that serial X-ray films should be taken to locate the spontaneous migration of catheters [7]. Even though the patient is asymptomatic and the device is functioning well, removal and replacement of the catheter is suggested when an improper position is identified.

Radiologists and surgeons have attempted to re-direct the tip of the external central venous catheter and Hickman catheter with a guide wire or Fogarty balloon catheter, whenever it is impossible to place a wire or catheter through the subcutaneous device [8-12]. Pasteur repositioned the catheter tip successfully by means of snaring the tip with a loop via a transfemoral approach. The catheter tip was pulled down from the internal jugular vein into the SVC [13]. This method can be used in cases of a migrated port catheter. However, if the cause of the catheter migration has not been determined and dealt with, migration could occur again. The definite cause of migration is unknown. It may be related to the position of the catheter, engorgement of the accessed vein with turbid blood flow, or the catheter material itself. In our two cases, no evidence of proximal obstruction of the accessed vein or venous engorgement with an abnormal blood flow could be demonstrated. The two catheters in our cases were relatively short, and the tips were at the junction of the innominate vein and the SVC. The ideal location of the catheter tip is reported to be the junction of the SVC and the right atrium, with the catheter directed vertically downward [14]. Krasnow re--ported that a short catheter would have an increased risk of spontaneous migration, if the catheter tip were placed only in the innominate vein or at the junction of the innominate vein and the SVC [15]. With catheters whose former location appears ideal, manipulation may be attempted. In patients with a previously malpositioned catheter or recurrent migration, removal and re-implantation are necessary. The catheter material may have some influence on the incidence of spontaneous migration. The majority of central venous catheters are made of polyvinylchloride (PVC), Teflon, polyurethane, or silicone. Silicone catheters are very flexible and cause less damage to the vascular tunica intima, but easily kink in the vessel, while polyvinylchloride and polyurethane catheters are somewhat rigid [16]. The spontaneously migrating catheters mentioned in many reports and in our cases have been silicone catheters [4,13,17-18].

The physician must be aware of the possible signs or symptoms of malpositioning. When any dysfunction of the IVAD is noticed, a chest X-ray film should be taken to determine the catheter position. Once the malpositioning of the catheter is recognized, the position should be corrected. Surgical intervention is suggested rather than non-operative management. Removal of the old catheter and its replacement with a new one will prevent recurrent migration and other possible severe complications.

References

1. Neiderhuber JE, Ensminger W, Gyves JW, *et al.* Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery 1982; 92: 706-12.
2. Lum PS, Soski M, Management of malpositioned central venous catheters. J intravenous Nurs 1989; 12; 356-65.
3. Krasnow SH, Rhodes G, Boyer M, *et al.* Hickman catheter placement. South Med J 1985; 78: 1327-9.
4. Vasquez RM, Brodski EG. Primary and secondary malposition of silicone central venous catheters. Acta Anesthesiol Scand 1985; 81: 22-5.
5. Gary R. Collin, Alis. Ahmadinejad, Edouard Misse. Spontaneous migration of subcutaneous central venous catheters.
6. Connoly J. Spreading cortical venous thrombosis due to infusion of hyperosmolar solution into the internal jugular vein. Br Med J 1982; 285: 935.
7. Van Haeften TW, Van Pampus ECM, Boot H, *et al.* Cardiac tamponade from misplaced central venous line in pericardiophrenic vein. Arch Intern Med 1988; 148: 1649-90.
8. Babikian G, Byron R, Hassett JM, Jr. Redirection of central venous pressure catheters using a flow-directed technique. Surg Gynecol Obstet 1986; 163: 483-4.
9. Carrasco CH, Richli WR, Charsangavej C, Wallace S. Technical note: Repositioning misplaced central venous catheters. Cardiovasc Intervent Radiol 1987; 10: 234-6.
10. Hawkins IF Jr, Paige RM. Redirection of malpositioned central venous catheters. Am J Radiol 1983; 140: 393-4.
11. Laufer E. Simple way to reposition a wandering central venous catheter. J Trauma 1985; 25: 438-9.
12. Schaefer CJ, Geelhoed GW. Redirection of misplaced central venous catheters. Arch Surg 1980; 115: 189-91.
13. Rasuli P, Hammond DI, Peterkin IR. Spontaneous intrajugular migration of long-term central venous access catheters. Radiology 1992; 182: 822-4.
14. Lois JF, Gomes AS. Pusey E. Nonsurgical repositioning of central venous catheters. Radiology 1987; 165: 329-33.
15. Krasnow SH, Rhodes G, Boyer M, *et al.* Hickman catheter placement. South Med J 1985; 78: 1327-9.
16. Sharon M. Weinstein. Plumer's Principles & Practice of Intravenous Therapy, Sixth Edition Chapter 12, 206-7.
17. Olcott EW, Gordon RL, Ring EJ. The injection technique for repositioning central venous catheter: Technical note. Cardiovasc Intervent Radiol 1989; 12: 292-3.
18. Passaro ME, Steiger E, Curtas S, Seidner DL. Long-term silastic catheter and chest pain. J Parenter Enteral Nutr 1994; 18: 240-2.

植入式血管裝置導管的自動漂移—兩個病例報告及文獻回顧

蔡建和 許瀚水 蘇維鈞 賴信良 王良順 黃敏雄

植入式血管裝置，有時被稱為“植入式注射座”，通常用於抽取血液樣本、給藥、輸液及營養的補充。有些併發症會導致此裝置功能不彰，我們描述了兩個少見的例子乃有關植入式血管裝置之導管的自動漂移。在第一個病例中，植入座的功能不佳並且注射時常常無法全速開啟，最後導致完全阻塞。在第二個病例中，植入座功能不佳且導管持續漂移。中央靜脈導管的漂移可以導致血管、神經、或感染等併發症，雖然有些作者報告可用非手術的方式矯正移位的中央靜脈導管，但很難將相同的方式應用於植入式注射座，因為這種裝置是完全埋於皮下的，在這種病例中，拔除原裝置及重新裝設通常是必需的。***(胸腔醫學 2004; 19: 109-114)***

關鍵詞：漂移，導管，植入式血管裝置

台北榮民總醫院 胸腔外科
索取抽印本請聯絡：許瀚水醫師，台北榮民總醫院胸腔外科，台北市石牌路二段 201 號

Video-Assisted Thoracoscopic Surgery for Mediastinal Parathyroid Adenoma — A Case Report and Literature Review

Chung-Wei Chen, Yih-Leong Chang, Yung-Chie Lee*

Primary hyperparathyroidism is the most common cause of hypercalcemia, and 25% of primary hyperparathyroidism is caused by ectopic mediastinal parathyroid glands [1]. In approximately 1-2% of the cases, the ectopic gland is in the mediastinum in a location that requires a thoracic approach [2]. A large hyperfunctioning parathyroid adenoma in the deep mediastinum is relatively rare, and may be safely resected using video-assisted thoracoscopic surgery to avoid an open surgical procedure. Only 28 patients who underwent video-assisted thoracoscopic surgical (VATS) resection of mediastinal parathyroid tumors have been reported in the world literature to date [1,3-5]. We herein describe our experience with the successful removal of a large anterior mediastinal parathyroid adenoma by video-assisted thoracoscopic surgery in a patient presenting with repeated ureteral stones. To our knowledge, this is the first reported case of thoracoscopic surgery for a mediastinal parathyroid adenoma in Taiwan [13-15]. ***(Thorac Med 2004; 19: 115-119)***

Key words: mediastinal parathyroid adenoma, video-assisted thoracoscopic surgery

Introduction

Most mediastinal parathyroid adenomas are situated in the upper mediastinum and most of them can be removed via a cervical approach. For the remaining cases, median sternotomy or thoracotomy is indicated to remove the tumors, but the procedures are associated with significant morbidity—up to 29% [6-7]. Thoracoscopic surgery for mediastinal parathyroid adenoma offers good access to the whole mediastinum. The currently available literature suggests that thoracoscopy is a safe and successful procedure for the resection of the mediastinal parathyroid. We herein report the first successful thoracoscopic resection of a mediastinal parathyroid adenoma in Taiwan.

Case Report

History and findings

A 78-year-old male patient with a medical history of DM and hypertension had suffered from repeated ureteral stones and chronic renal insufficiency for 4 years prior to this admission. He visited the urology clinic first for his back pain, and was treated with extracorporeal shock wave lithotripsy for ureteral stones at the age of 74. However, persistent hypercalcemia was noted during the OPD

Division of Thoracic Surgery, Departments of Surgery and Pathology, National Taiwan University Hospital and National Taiwan University College of Medicine, No. 7, Chung-Shan South Road, Taipei, Taiwan
Address reprint requests to: Dr. Yung-Chie Lee, Department of Surgery, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan

follow-up, with a serum calcium concentration of 2.67mmole/L (normal range = 2.1-2.6mmole/L), a phosphate level of 4.8mg/dL (normal range = 2.5-4.5mg/dL), and an increased parathyroid hormone level of 261pg/ml (normal range = 10-50pg/ml). Cervical ultrasonography and a standard chest roentgenogram showed no abnormal finding. Technetium-99m sestamibi scintigraphy revealed increased activity in the left upper mediastinum (Figure 1). Computed tomography (CT) of the chest confirmed a tumor within the anterior mediastinum with innominate vein compression (Figure 2). Thus, a diagnosis of primary hyperparathyroidism secondary to a mediastinal parathyroid adenoma was made. He denied bone pain, easy fatigue, or constipation.

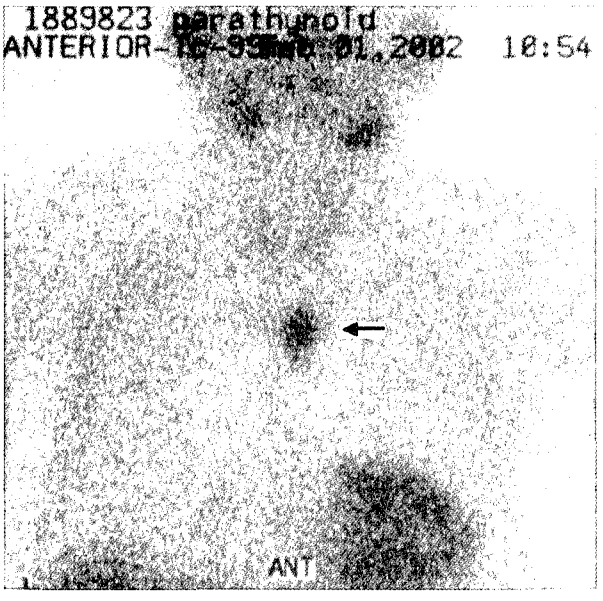

Fig 1. Tc99m sestamibi scan reveals an abnormal uptake in the mediastinum (arrow). Normal uptake in thyroid is seen

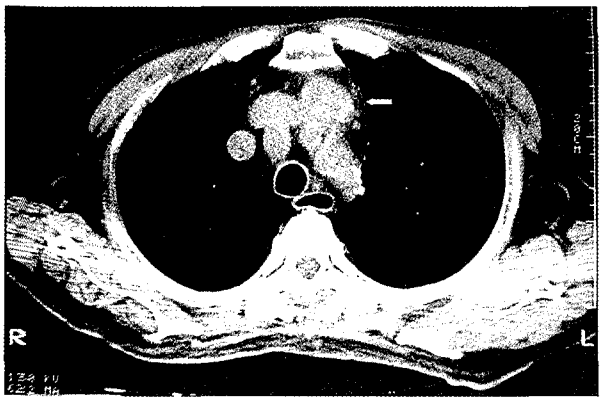

Fig 2. Chest CT scan shows a 3 cm tumor on the anterior mediastinum (hollow arrow) with compression of the innominant vein.

On physical examination, he appeared to be chronically ill. The lungs, heart, and abdomen were normal. There was no skin rash or peripheral edema. On neurologic examination, the patient was alert and well oriented, with intact speech. No focal neurologic deficit was presented.

Operative procedure

The patient was operated on a right decubitus position with general anesthesia and one-lung ventilation (double lumen tube). Three trocars were emplaced, one each in the midaxillary line at the third intercostal space, the anterior axillary line at the 6th intercostal space, and the posterior axillary line at the 7th intercostals space, forming a triangle. The procedure was assisted with a standard 10-mm rigid telescope with a 30° angle. After identifying the mass sitting on the innominate vein in close vicinity to the aortic arch and phrenic nerve, the mediastinal pleura was incised longitudinally, followed by a blunt and partly sharp dissection of the mass. The phrenic nerve was preserved. Small vessels were clipped or coagulated. Finally, the proximal end of the tumor, which seemed to be connected to the thymus gland, was clipped and the tumor was resected. A chest tube was introduced through the camera port.

The resected specimen in the anterior mediastinum measured 4.5 x 4.0 x 2.5 cm. Histologic examination of the resected specimen confirmed the diagnosis of a parathyroid adenoma (Figure 3).

Postoperative course

The patient's postoperative recovery was uneventful and the chest tube was removed on postoperative day 10. Transient hypocalcemia normalized within 14 days, and the parathyroid hormone level then dropped to 20.8pg/ml. The patient received an AV shunt operation on postoperative day 20, to undergo hemodialysis. There have been no signs of

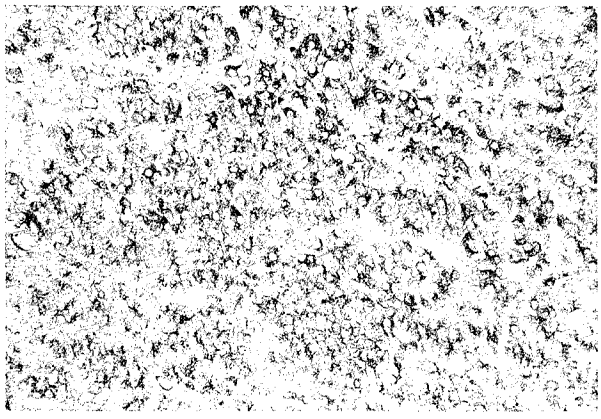

Fig. 3. Histological features of the parathyroid adenoma showing islands of parathyroid chief cells with focal clear cell change, which is evidenced by a positive parathyroid hormone stain.

respiratory symptoms, nor clinical nor laboratory evidence of a recurrence of hyperparathyroidism during OPD following-up.

Discussion

Hyperparathyroidism may be primary or secondary. Hyperfunctioning mediastinal parathyroid tumors, although unusual, are found in 20% to 25% of all those patients with primary hyperparathyroidism [8]. Parathyroid tumors are usually small and well encapsulated. The noninvasive imaging studies commonly used for parathyroid localization are ultrasound (US), technetium-99m sestamibi scintigraphy (Tc99m MIBI), and bolus-enhanced computed tomography (CT). Because of its excellent sensitivity (80-95%) and specificity (95%), Tc99m MIBI is recommended as the best single screening study in patients who are suspected of having ectopic parathyroid lesions [9]. When lesions prove to not be accessible through a cervical approach, a median sternotomy or thoracotomy has been considered an option for removal. The reported incidence of median sternotomies for all patients with primary hyperparathyroidism ranges from 1.4% to 14% [10]. However, sternotomy for removal of ectopic parathyroid tissue has a 19% to 29% complication rate, including pulmonary complications (effusions, pneumonitis, and pneumothorax), wound complications, deep venous thrombosis, and atrial fibrillation [6-7].

Since the advent of endoscopic surgery, various procedures have been used for the removal of mediastinal parathyroid adenomas, including thoracoscopic [3], transcervically mediastinoscopic [11], and subxiphoidally laparoscopic [12] excisions. We suggest the thoracoscopic exploration of selected mediastinal parathyroid tumors as an alternative to more invasive surgical approaches. In comparison to sternotomy, thoracoscopy offers the same benefits as surgical resection, with the added potential of a marked decrease in general morbidity and a superior cosmetic result. Thoracoscopy allows better visualization than the cervical approach, and the subxiphoid approach would not seem to offer any significant advantages over VATS. A total of 28 patients who underwent video-assisted thoracoscopic surgery (VATS) resection of mediastinal parathyroid tumors have been identified in the literature [1,3-5]. Parathyroid adenomas situated anywhere in the mediastinum can be approached and removed using thoracoscopy. The currently available literature suggests that thoracoscopy is a safe and successful procedure for the resection of the mediastinal parathyroid. The success of VATS depends on accurate localization before operation, with little use of intraoperative localization other than direct visualization.

Conclusion

We report a case of a large mediastinal parathyroid adenoma resected successfully using a thoracoscopic approach. The patient recovered quickly and no symptoms of recurrence of hyperparathyroidism were evident. We believe that the thoracoscopic approach may reduce morbidity, in addition to providing tissue for histopathological diagnosis and shortening the hospital stay, compared with the conventional sternotomy.

References

1. Ott MC, Malthaner RA, Reid R, Intraoperative radioguided

thoracoscopic removal of ectopic parathyroid adenoma Ann Thorac Surg 2001; 72(5): 1758-60.

2. Dadan J. Dziecio J. adny JR. Hady HR. Puchalski Z. Surgical treatment of primary and secondary hyperparathyroidism Przeglad Lekarski. 2002; 59(2): 84-7.
3. Lesser T, Bartel M. Videothoracoscopic excision of mediastinal parathyroid adenoma. Eur J Surg 1999; 165: 395-7.
4. Kumar A. Kumar S. Aggarwal S. Kumar R. Tandon N. Thoracoscopy: the preferred method for excision of mediastinal parathyroids. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques. 2002; 12(4): 295-300.
5. O'Herrin JK. Weigel T. Wilson M. Chen H. Radioguided parathyroidectomy via VATS combined with intraoperative parathyroid hormone testing: the surgical approach of choice for patients with mediastinal parathyroid adenomas? Journal of Bone & Mineral Research, 2002; 17(8): 1368-71.
6. Norton JA, Schneider PD, Brennan MF: Median sternotomy in reoperation for primary hyperparathyroidism. World J Surg 1985; 9: 807-10.
7. Conn JM, Goncalves MA, Mansour KA, *et al.* The mediastinal parathyroid. Am Surg 1991; 37: 62-6.
8. Nathaniels EK, Nathaniels AM, Wang C: Mediastinal parathyroid tumors: a clinical and pathological study of 84 cases. Am Surg 1970; 171: 165.
9. Moinuddin M,Whynott C. Ectopic parathyroid adenomas: multi-imaging modalities and its management. Clin Nucl Med 1996; 21: 27-32.
10. Wang CA, Gaz RD, Moncure AC: Mediastinal parathyroid exploration: A clinical and pathological study of 47 cases. World J Surg 1986; 10: 687-95.
11. Deeb ME. Brinster CJ. Kucharzuk J. Shrager JB. Kaiser LR. Expanded indications for transcervical thymectomy in the management of anterior mediastinal masses. Ann Thorac Surg. 2001; 72(1): 208-11.
12. Wei JP, Gadacz TR, Weisner LF, *et al.* The subxiphoid laparoscopic approach for resection of mediastinal parathyroid adenoma after successful localization with Tc99m-sestamibi radionuclide scan. Surg Laparosc Endosc 1995; 5: 402-6.
13. 王超群，王明誠，宋俊明等：合併原發性與次發性副甲狀腺機能亢進症—病例報告，內科學誌 2000; 11 (2)。
14. 許雅玲，賴史明，陳雁玲等：原發性副甲狀腺機能亢進症合併高血鈣危症：一病例報告暨文獻回顧，內科學誌 2000; 11(5)。
15. 陳振雄，王佩文，劉瑞川等：異位副甲狀腺腺瘤併嚴重骨骼飢餓症候群：一例報告，長庚醫誌 1996; 19(2) 196-202 。

胸腔鏡手術治療縱膈腔副甲狀腺瘤：一病例報告及文獻回顧

陳忠蔚　張逸良*　李元麒

原發性副甲狀腺機能亢進是造成高血鈣血症最常見的原因，約有 25% 原發性副甲狀腺機能亢進是由縱膈腔副甲狀腺瘤引致。在這些異位性縱膈腔副甲狀腺瘤的病例當中，約有 1 － 2% 需要採開胸手術切除，然而開胸手術伴隨有相當比例的合併症（19 － 29%）。隨著內視鏡手術的發達，各種不同的內視鏡技術已經陸續應用在縱膈腔副甲狀腺腫瘤的切除上，包括胸腔鏡，縱膈腔鏡及劍凸下腹腔鏡手術。胸腔鏡手術因為發展較早及視野良好而最多人採用，胸腔鏡手術除了可以有效避免開胸手術所帶來的大傷口及合併症外，截至目前為止文獻上記載的 28 例胸腔鏡手術切除縱膈腔副甲狀腺腫瘤案例，均能順利完成手術。

我們報告一個七十八歲的男性病例，在 4 年來他因為反覆尿路結石接受了震波碎石術並有慢性腎衰竭症狀。經門診驗血發現有高血鈣血症及副甲狀腺機能亢進（副甲狀腺素濃度 261 pg/ml；正常值 = 10-50 pg/ml）。頸部超音波無異常發現，鉈 99m 掃描於縱膈腔發現有異常顯影並且在電腦斷層攝影發現有前縱膈腔腫瘤，患者接受了胸腔鏡手術切除縱膈腔副甲狀腺腫瘤，術後復原良好且血鈣及副甲狀腺素濃度均恢復正常，截至目前為止並無腫瘤再復發的情形發生。***(胸腔醫學 2004; 19: 115-119)***

關鍵詞：縱膈腔副甲狀腺腫瘤，胸腔鏡手術

台大醫院　胸腔外科　病理科*
索取抽印本請聯絡：李元麒醫師，台大醫院胸腔外科，台北市中山南路七號

Primary Lymphoepithelioma-Like Carcinoma of the Lung — A Case Report

Xian-Yuan Guo, Cheng-Ping Yu *, Yeung-Leung Cheng, Shih-Chun Lee

Primary lymphoepithelioma-like carcinoma of the lung is a neoplasm seen most commonly in the nasopharynx of individuals from south China and Taiwan that is strongly associated with the Epstein-Barr virus. A 46-year-old Chinese woman presented with clubbed fingers and toes for one year and hemoptysis for more than one year. She was admitted to our hospital with a suspicious lesion in the left lower lobe of the lung. The patient was treated with surgical resection and diagnosed with primary lymphoepithelioma-like carcinoma of the lung. These symptoms resolved themselves 6 months later. ***(Thorac Med 2004; 19: 120-124)***

Key words: lymphoepithelioma-like carcinoma, Epstein-Barr virus, lung, lobectomy

Introduction

The first description of a patient with a lymphoepithelioma-like carcinoma (LELC) of the lung was made by Begin and associates in 1987 [1]. Although lymphoepithelioma-like carcinoma most commonly occurs in the nasopharynx, it can arise in a variety of sites, including the salivary gland, thymus, lung, stomach, and skin [2]. Primary LELC of the lung is very rare, and scant information is available in the literature. Most of the reported cases of LELC of the lung have occurred in patients of Asian descent, especially those from Southeastern China. LELC of the lung is strongly associated with EBV infection in Asian patients [3]. The relationship between the LELC and EBV, and the principles of treatment, are discussed in this paper.

Case Report

A 46-year-old Chinese female living in Taiwan was admitted to the hospital in May 2002, due to clubbing of the fingers and toes, and hemoptysis for more than one year. A chest radiograph showed a large pulmonary mass located in the left lower lobe (LLL) (Figure 1). A large, circumscribed, soft tissue mass (approximately 10.5 x 9.0 x 7.0 cm) was found in the LLL of the lung on a contrast-enhanced computed tomography (CT) scan (Figure 2). The tumor mass grew rapidly and increased more than twofold in size during a 6-month period. There was no evidence of calcification or fat content in the lung, and no lymphadenopathy in the mediastinum and hilar regions. The patient underwent bronchoscopy with bronchial brushing and CT-guided lung biopsy. The bronchial brushing culture showed tuberculosis (TB), and the report of the CT-guided lung biopsy showed chronic inflammation. Except for clubbing of the fingers and toes, there were no remarkable physical examination findings

Division of Thoracic Surgery, Department of Surgery, and *Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.
Address reprint requests to: Dr. Xian-Yuan Guo., Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital, No. 325, Sec. 2, Cheng-Gung Road, Nei-Hu, Taipei, Taiwan 114, R.O.C.

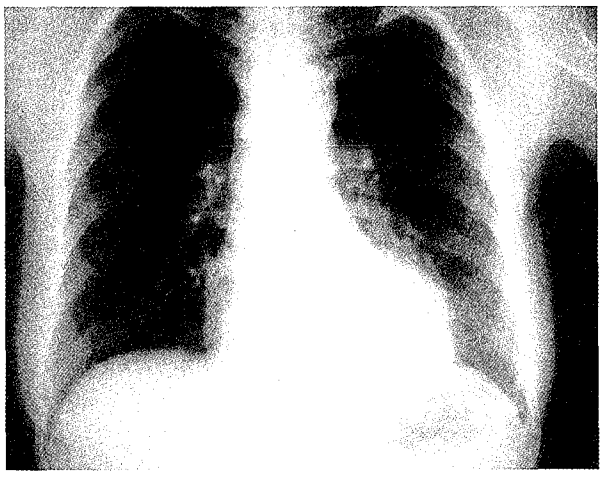

Fig. 1. Chest radiograph showed that a large pulmonary mass was located in the left lower lobe.

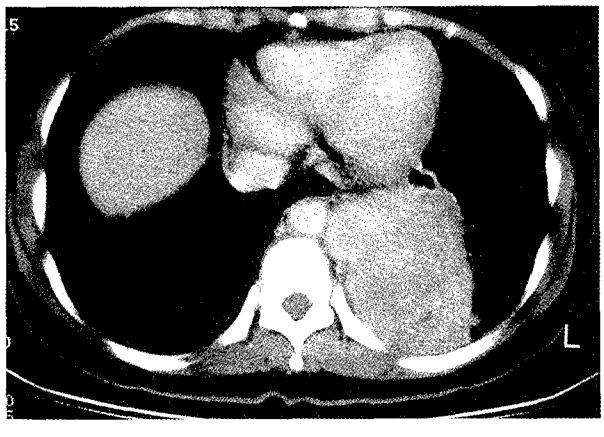

Fig. 2. Chest CT scan at admission showing a large, ill-defined, heterogeneous, circumscribed soft tissue mass (approximately 10.5 x 9.0 x 7.0 cm) on the left lower lobe.

upon admission. The results of routine blood tests, clinical biochemical analyses, and tests for known tumor markers were within normal limits, except for a critically high alkaline phosphatase level (639 U/L; normal range: 64-306 U/L).

Treatment for TB was given for 4 months before the operation. The patient underwent preoperative bronchoscopy, but no significant intraluminal anomaly was found. A lobectomy of the left lower lobe, with a lymph node dissection, was performed since malignancy of lung could not be ruled out. A solid tumor, 7 x 7 x 6 cm, was located in the basal segment of the LLL, with diaphragmatic and

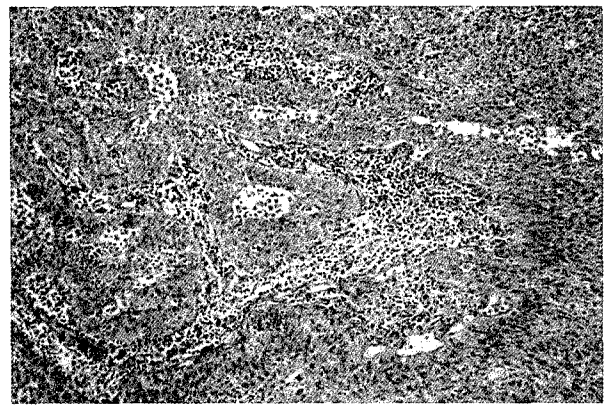

Fig. 3. Poorly differentiated neoplastic cells arranged in solid sheets and nests with pleomorphic vesicular nuclei and prominent nucleoli. There was heavy lymphoplasmacytic reaction surrounding and infiltrating the tumor nests (H&E 200X).

descending aortic adventitia adhesion. There were enlarged lymph nodes in the aorto-pulmonary window, and lower paratracheal and hilar regions.

Histologically, the tumor was composed of poorly differentiated neoplastic cells arranged into solid sheets and nests. The tumor cells were large, with pleomorphic vesicular nuclei and prominent nucleoli. There was a heavy lymphoplasmacytic reaction surrounding and infiltrating the tumor nests (Figure 3). Immunohistochemistry revealed that the tumor cells were positive for cytokeratin, but negative for leukocyte common antigen. In the non-neoplastic lung, there was a granulomatous inflammation lesion with caseous necrosis and Langhan's giant cells. Although an acid-fast stain was negative for tuberculosis bacillus, the observed characteristics were still consistent with tuberculosis. The hilar nodes showed tuberculous lymphadenitis, but no sign of tumor invasion. The bronchial margins were free of tumor invasion. Immunohistochemistry for EBV-associated protein LMP1 revealed focal reaction for the tumor cells, but not the lymphocytes (Figure 4). The post-operative course was not complicated and the patient was discharged 12 days later. The symptoms of clubbed fingers and toes resolved 6 months later.

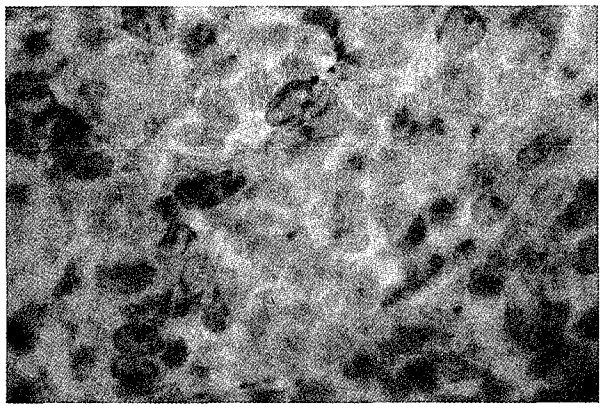

Fig. 4. Poorly differentiated tumor cells are focally reactive for EBV-LMP1 protein (Immunohistochemistry, 400X).

Discussion

Lymphoepithelioma is an undifferentiated carcinoma with prominent lymphoid stroma in the nasopharynx. Tumors with similar histology have been reported with other localizations, including the lungs, and are designated as lymphoepithelioma-like carcinomas. LELC is a non-nasopharyngeal undifferentiated carcinoma with prominent lymphoid infiltration [4].

A clinicopathologic study was done of 11 patients with LELC. The patients were between 38 and 73 years of age (median, 54 years), with an equal sex incidence [2]. The patients presented with cough, bloodstained sputum, and pleural effusion. Most often, tumors were incidentally discovered, and appeared as peripheral coin lesions in the chest X-ray. The tumors presented with nearly the same frequency in both lungs. The lesions usually presented as a solitary subpleural nodule, and there was no strong association with cigarette smoking [2]. Lymph node metastases were found in approximately 25% of the cases.

Most patients with LELC presented with early stage disease. The behavior of LELC of the lung is highly variable, ranging from apparent curability by excision (particularly for localized disease) to highly aggressive, extensive disease at presentation [2]. LELC tends to affect young non-smoking Asians, and is often resectable [5]. In most cases, a lobectomy is performed. Hematogenous metastases seldom occur, and are observed almost exclusively in the skeletal system [6].

There is a potential oncogenic relationship between EBV and LELC of the lung. LELC may be closely associated with EBV infection in tumorigenesis [7]. EBV infection may precede the clonal expansion of the tumor. The characteristic histopathology of the tumor cells, together with their pattern of immunohistochemical staining, is helpful in distinguishing LELC from the differential diagnoses (includinge granulomatous inflammatory diseases [especially tuberculosis], malignant lymphoma, melanoma, and metastatic sarcoma). The distinctive histopathologic features consist of cohesive sheets and clusters of polygonal tumor cells, which possess moderately pleomorphic vesicular nuclei and prominent nucleoli that are intimately intermixed with numerous small lymphocytes [8]. Tumors consist of solid nests of undifferentiated tumor cells in a syncytial arrangement, surrounded by heavy lymphoplasmacytic infiltrates. Tumor cells usually stain positive for keratin but negative for leukocyte common antigen [3].

The patient in this study presented with clubbed fingers and toes; these extrathoracic symptoms resolved themselves after resection of the tumor. Extrathoracic sites are affected by one or more biologic or biochemical substances produced by the lung tumor. The various extrathoracic effects are grouped into paraneoplastic syndromes, which occur in about 2% of patients. Plain radiographs of the affected bones demonstrate hypertrophic pulmonary osteoarthropathy characterized by a proliferating periostitis of the distal ends of the long bones, particularly the tibia, the fibula and the radius. Owing to the periostitis, alkaline phosphatase levels are often elevated, but serum hepatic enzyme levels are normal [9]. The patient reported herein had the same situation during hospitalization. The patient in this case study was alive without evidence of tumor recurrence at 6 months after the operation and the alkaline phosphatase levels had returned to normal (167 U/L).

References

1. Begin LR, Eskandari J, Joncas J, *et al.* Epstein-Barr virus-related lymphoepithelioma-like carcinoma of the lung. J Surg Oncol 1987; 36(4): 280-3.
2. Chan JK, Hui PK, Tsang WY, *et al.* Primary lymphoepithelioma-like carcinoma of the lung: a clinicopathologic study of 11 cases. Cancer 1995; 76(3): 413-22.
3. Castro CY, Ostrowski ML, Barrios R, *et al.* Relationship between Epstein-Barr virus and lymphoepithelioma-like carcinoma of the lung: a clinicopathologic study of 6 cases and review of the literature. Hum Path. 2001; 32(8): 863-72.
4. Barroso A, Nogueira R, Lencastre H, *et al.* Primary lymphoepithelioma-like carcinoma of the lung. Lung Cancer 2000; 28(1): 69-74.
5. Ho JC, Lam WK, Ooi GC, *et al.* Chemoradiotherapy for advanced lymphoepithelioma-like carcinoma of the lung. Respir Med 2000; 94(10): 943-7.
6. Wockel W, Hofler G, Popper HH, *et al.* Lymphoepithelioma-like lung carcinomas. Pathologe 1997; 18(2): 147-52.
7. Han AJ, Xiong M, Zong YS. Association of Epstein-Barr virus with lymphoepithelioma-like carcinoma of the lung in southern China. Am J Clin Pathol 2000; 114(2): 220-6.
8. Chow LT, Chow WH, Tsui WM, *et al.* Fine-needle aspiration cytologic diagnosis of lymphoepithelioma-like carcinoma of the lung. Report of two cases with immunohistochemical study. Am J Clin Pathol 1995; 103(1): 35-40.
9. Maddaus MA, Ginsberg RJ. Clinical features, diagnosis, and staging of lung cancer. In: Pearson FG, Cooper JD, Deslauriers J, Ginsberg RJ, Hiebert CA, Patterson GA, Urschel HC, editors. Thoracic Surgery 2nd ed. New York: Churchill Livingstone 2002; 813-36.

原發性肺類淋巴上皮癌—病例報告

郭獻源　程永隆　于承平*　李世俊

原發性類淋巴上皮癌於中國南方及台灣之病患中常伴隨有 Epstein-Barr 病毒感染，但一般與此病毒感染之相關腫瘤常見於鼻咽腔。此報告為一位四十六歲台灣女性，其手指及腳趾呈現為杵狀有一年之時間，且偶而咳血有超過一年之久，因發現病患左下肺葉有一疑似肺腫塊而住院治療，經接受手術切除治療，此病灶最後診斷為原發性肺類淋巴上皮癌，前述症狀於手術後六個月完全消除。***(胸腔醫學 2004; 19: 120-124)***

關鍵詞：原發性類淋巴上皮癌，Epstein-Barr 病毒，肺，肺葉切除

內湖三軍總醫院　胸腔外科　病理部 *
索取抽印本請聯絡：郭獻源醫師，內湖三軍總醫院胸腔外科，114 臺北市內湖區成功路二段 325 號

Mediastinal Hemangiomatosis — A Case Report

Wei-Jin Chan, Kuo-Chen Cheng, Jiunn-Min Shieh, Yoau Fong*,
Jinn-Ming Chang**, Shih-Sung Chuang***, Shian-Chin Ko

Hemangiomas are benign vascular neoplasms that most commonly occur in the skin, subcutaneous tissue, mucous membranes of the oral and genital regions, and abdominal viscera. Multiple hemangiomas are defined as hemangiomatosis. The majority of hemangiomas require no intervention, however, treatment is necessary in 10% to 20% of cases, due to their location, size, or behavior. The diagnosis of life-threatening hemangiomas base on radiographic studies is challenging because the hemangiomas might mimic other lesions or carcinomas. They are typically not diagnosed until surgery. In this case, we report an 18-year-old patient who had suffered from dyspnea and chest pain for several years. Chest radiographs showed a mediastinal mass that initial CT-guided biopsy reported as a thymoma. However, the definitive diagnosis, after open lung biopsy, turned out to be mediastinal hemangiomatosis. ***(Thorac Med 2004; 19: 125-131)***

Key words: hemangiomas, hemangiomatosis, thymoma

Introduction

Hemangiomas are benign vascular neoplasms that exhibit an early and rapid proliferative phase during the first year of life. They are characterized by the canalization of hyperplastic solid masses of endothelial cells, followed by a slower involution phase that may last for years [1]. Hemangiomas most commonly occur in the skin, subcutaneous tissue, mucous membranes of the oral and genital regions, and abdominal viscera [1-3]. The majority of hemangiomas require no intervention. However, treatment is necessary in 10% to 20% of cases, due to their location, size, or behavior [4]. Diagnosis of life-threatening hemangiomas from radiographic studies is challenging: they are typically not diagnosed until surgical intervention.

Case Report

This 18-year-old boy presented with exertional dyspnea and intermittent chest pain radiating to the back for several years. No other respiratory symptoms, such as cough or hemoptysis, or systemic symptoms, such as fever or body weight loss, were noted. He went to our outpatient clinic, where chest radiography showed a widening of the upper mediastinum and increased linear opacities in bilateral basal lungs (Figure 1). He was admitted to the chest medicine division for further investigation.

In tracing the patient's past medical history, we found he had received a splenectomy at age 4 due to a splenic hemangioma causing disseminated intravascular coagulation. A recision of multiple

Division of Chest Medicine, *Division of Chest Surgery, **Department of Radiology, ***Department of Pathology, Chi Mei Medical Center, Tainan, Taiwan
Address reprint requests to: Dr. Shian-Chin Ko, Division of Chest Medicine, Department of Internal Medicine, Chi Mei Medical Center, 901, Chuang Hua Road, Yung Kang City, 710 Tainan, Taiwan

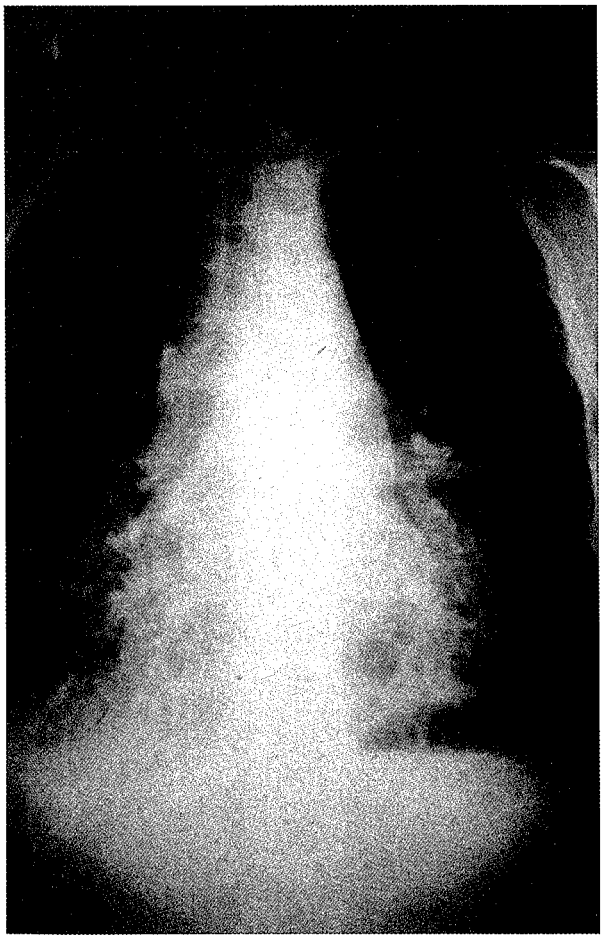

Fig. 1. Chest radiography shows a widening of the upper mediastinum and increased linear opacities in bilateral basal lungs.

hemangiomas on the occipital scalp and a hemangioma on the back was also done at age 13. He underwent a tonsillectomy and uvulopalatopharyngoplasty due to obstructive sleep apnea syndrome at age 15.

On physical examination, a decrease in breathing sounds was observed in the left chest region. The pulmonary function test reported moderately obstructive ventilatory impairment without significant bronchodilator reversibility. Sputum culture and cytologic studies showed negative findings. Chest computerized tomography (CT) revealed diffuse infiltrates of soft tissue densities in the bilateral hila and throughout the mediastinum. Multiple reticulo-nodular densities, diffuse prominent bronchovascular bundles, and interlobular septal thickening were also noted in bilateral lung fields (Figure 2). CT-guided needle biopsy of the mediastinal mass showed a nodular pattern of mixed round-shaped epithelial cells and lymphocytes, and some dilated vessels. The epithelial cells were highlighted by immunostaining with cytokeratin (AE1/AE3). The vascular channels were overlooked and the initial, although erroneous, pathologic diagnosis was thymoma. The patient was transferred for surgical intervention.

He received a minithoracoectomy in January 2003. A plaque-like lesion rather than a mass was seen in the mediastinum. Multiple engorged vascular lesions were also noted in the pulmonary parenchyma. Severe bleeding during pericardial biopsy

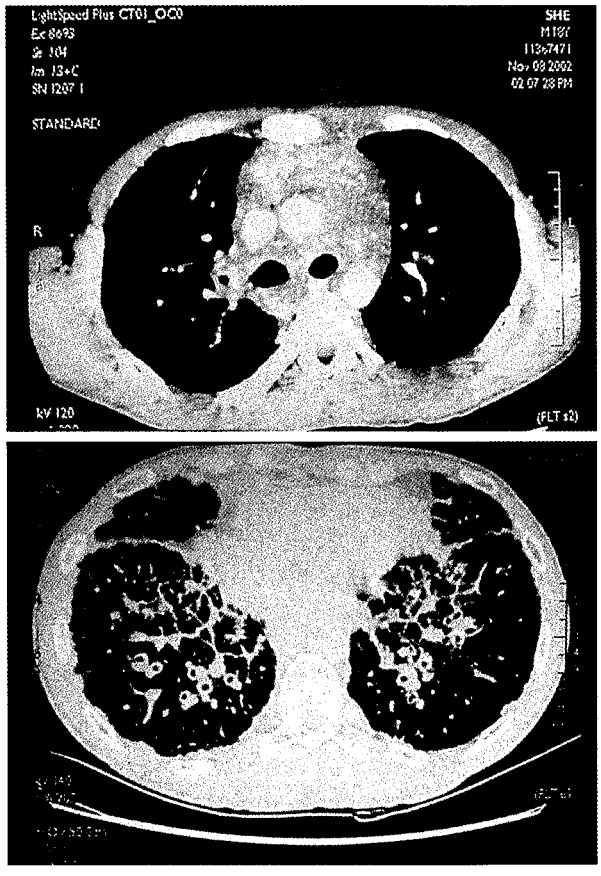

Fig. 2. Chest computerized tomography (CT) reveals: (1) Diffuse interstitial thickness and nodulation mainly in the interlobular septum. (2) Irregular thickness in the bronchovascular bundles, and subpleural surface of the bilateral lungs. (3) Widening of the mediastinum with diffuse veining opacities, consistent with hypervascularity.

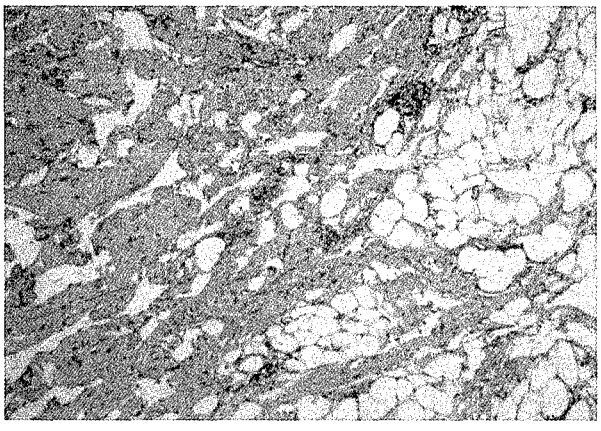

Fig. 3. Photomicrography of the pericardium shows interconnecting capillary channels within fibroadipose tissue (HE stain).

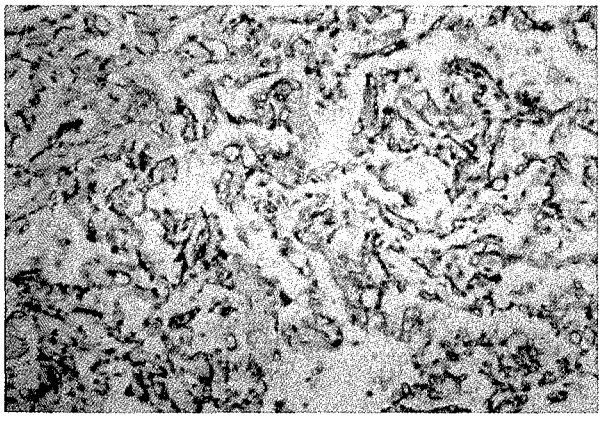

Fig. 4. Photomicrography of the pericardium stained with CD34 highlights the endothelial cells (immunohistochemical stain).

occurred. Lung wedge resections in the left upper and left lower lobes, and a pericardial biopsy, were performed. Microscopically, the specimens from the pericardium and pulmonary parenchyma showed a similar picture, that is, of a capillary hemangioma with an aggregate of capillaries with focal hemorrhage (Figure 3). The endothelial cells were highlighted with CD34-immunostaining (Figure 4). The definitive diagnosis was hemangiomatosis.

The patient was then referred to the oncology division for further radiation treatment.

Discussion

Hemangioma is a primary tumor of the microvasculature in which angiogenesis is initially excessive, followed by a regression of the newly formed vessels. Their histological components include capillary endothelial cells along with an accumulation of macrophages, plasma cells, pericytes, and mast cells [4]. Hemangiomas have a predilection toward females rather then males, at rate of 3:1, and occur in nearly 1-2% of newborns and 10-12% of infants by one year of age [1,5-7].

Hemangiomas limited to the skin have a good prognosis since they usually undergo involution within the first 2 years of life. Fifty percent of the lesions resolve themselves by 5 years of age, and 70% by 7 years of age [1,5,8-9]. The most commonly affected sites are the head and neck, followed by the trunk and limb. When hemangiomas occur in the orbit or adnexa, the complications include astigmatism, anisometropia, amblyopia, and strabismus [1,5-6]. If the subglottalic region is involved, the patient will most probably suffer from respiratory failure, especially infants of 6 to 12 weeks old. Hoarseness and stridor are the signs of subglottalic hemangiomas [5-6]. If the hemangiomas involve the visceral organs, the morbidity and mortality rates are high (40-80%), because of the complications of high-output cardiac failure, gastro-intestinal bleeding, anemia, obstructive jaundice, seizures, hydrocephalus, and consumptive coagulopathy [1-2,5-6, 8,10-11]. Multiple congenital hemangiomas that affect the skin and viscera have been defined as diffuse neonatal hemangiomatosis [1-2,8]. The most commonly involved visceral organ is the liver (60-100%), followed by the lung (52%), brain (52%), and intestine (52%) [1-2,8,10-11]. Hemangiomas also involve the lymph nodes, spleen, kidney, iris, retina, salivary glands, heart, thymus, bladder, gallbladder, pancreas, and adrenal gland [1].

The diagnosis of hemangiomatosis by radiographic imaging can determine the extent and location of the involvement [9]. Ultrasonography with Doppler studies demonstrates the high flow pattern that is the characteristic of hemangiomas [6]. On CT scanning, hemangiomas appear as a homogeneous mass [6]. Magnetic resonance imaging of hemangiomas has shown well-circumscribed,

densely lobulated masses, with an intermediated signal intensity on T_1 -weighted images [6,9]. However, the diagnosis of hemangiomas of the internal organs by radiographic imaging or CT-scan is somewhat challenging, since the hemangiomas might mimic other lesions or carcinomas. Raymond et al. mentioned that internal hemorrhoids, adenomatous polyps, carcinoma, inflammatory bowel disease, and proctitis, might all mimic diffuse cavernous hemangiomas [12].

In this case, we mistook the mediastinal mass for a thymoma, and lymphangitis carcinomatosis was also suspected, base on the CT findings. However, the specimen from the open lung biopsy showed plaque-like lesions rather than a mass. Severe bleeding was also noted during pericardial biopsy, with multiple engorged vascular lesions in the pulmonary parenchyma. Thus, mediastinal hemangiomatosis was highly suspected.

From the past medical history, we knew that the patient had had splenic hemangioma and multiple cutaneous hemangiomas in the past. The pathologic results this time showed hemangiomatosis of the pericardium and lung. We believe that this 18-year-old boy has diffused neonatal hemangiomatosis (DNH), a rare condition characterized by multiple benign cutaneous and visceral hemangiomas.

As mentioned above, the diagnosis of hemangiomas in the visceral organs, using radiography only, may occasionally be difficult. In this case, the mediastinal mass was misdiagnosed as a thymoma initially, using CT-guided biopsy, because the cytokeratin stain highlighted the thymic epithelial cells which mimicked a thymoma; besides, the thymoma is the most common tumor of the anterior mediastinum. After surgical intervention, we reviewed the previous CT-guided biopsy specimen again. Microscopically, multiple small vascular channels lined with endothelial cells were present between the hyperplastic thymic tissue and thymic epithelial cells, admixed with small lymphocytes. Thus hyperplasia of the thymic tissue can be misinter-preted as a thymoma.

Our patient had dyspnea, and his chest films showed a widening of the upper mediastinum and increased linear opacities in bilateral basal lungs, mimicking bronchiectasis. Chest CT scanning showed multiple nodularities with diffuse bronchovascular bundles and interlobular septal thickening in the bilateral lung field. These findings were quite similar to pulmonary capillary hemangiomatosis (PCH) and pulmonary veno-occlusive disease. The characteristic anatomic abnormality in pulmonary veno-occlusive disease is obstruction of the pulmonary veins and venules by intimal fibrosis, cellular proliferation, and muscularization [13]. Pulmonary capillary hemangiomatosis is characterized by thin-walled microvessels infiltrating the peribronchial and perivascular interstitium, lung parenchyma, and septal or pleural connective tissue [13-14]. Secondary pulmonary veno-occlusive disease might occur, resulting in the infiltration and compression of the pulmonary vein by these microvessels [13]. Following a slow, progressive clinical course, PCH will lead to pulmonary hypertension, hemoptysis, and right heart failure [14-15].

The pathogenesis of hemangiomas is unclear, and is believed to be related to hormonal influences and cellular markers of angiogenesis [5-6,11]. Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), and interleukin-6 (IL-6) are the regulators of angiogenesis, and may be involved in the proliferation and involution of hemangiomas [4].

The majority of hemangiomas need no intervention. Treatment is considered based on the location and size of the lesions, the presence of complications, the rate of growth or involution of the lesions, and the age of the patient [1,5-6]. When hemangiomas interfere with important structures and their functions, active treatment is necessary [1]. There are various therapeutic modalities, including systemic corticosteroids, interferon-α-2a, arterial embolization, surgical excision, cryotherapy, cytotoxic agents, laser treatment, and radiation [1-2,4-5]. High-dose systemic or intralesional steroid is the first-line treatment, and a dramatic response has been observed in 30% of cases [1,4]. Interferon-α-2a, an inhibitor of angiogenesis, is recommended for the treatment of life-threatening

hemangiomas that fail to respond to corticosteroid therapy [5-6,9]. The mechanism of action of interferon-α-2a is the inhibiting of the response of endothelial cells, smooth muscle cells, and fibroblasts to their respective growth factors [2]. So the proliferation and migration of endothelial cells is inhibited [14]. Arterial embolization is used to treat cutaneous hemangiomas that have not responded to medical therapy [6]. Cryotherapy and laser treatment are used for the treatment of superficial hemangiomas [5-6]. Radiation was the primary treatment used for hemangiomas during the 1940s and 1950s [5-6]. Surgical excision could be considered for hemangiomas that are life-threatening or impair function, and for which pharmocologic therapy is not effective or well tolerated. However, the benefits and risks of the surgery must be weighed carefully. There might be a high risk of bleeding, and the scar formation may be worse than the result of a spontaneous involution [5-6].

In our case, the patient was referred to the oncology department for radiation therapy. The dyspnea on exertion had resolved by the time of the later follow-up. The mediastinal hemangiomatosis lesions had been restricted and mildly reduced in size. His condition became satisfactory, and he received regular outpatient follow up.

Conclusions

Hemangiomas are benign vascular neoplasms and usually regress spontaneously. Multiple congenital hemangiomas that affect the skin and viscera, known as diffuse neonatal hemangiomatosis, may be fatal. As in our case, hemangiomatosis may involve the lungs, mediastinum, and pericardium, mimicking a mediastinal tumor and lymphangitis carcinomatosis in the radiographic findings. Since the important traits of hemongiomatosis are multiple and recurrent, tracing past medical history is mandatory. The definitive diagnosis relies on histological findings through surgical intervention.

References

1. Baska EB, Baykara M, Saricaoglu H, *et al.* Benign neonatal hemangiomatosis with conjunctival involvement. Report of a case and review of the literature. Acta Derm Venereol 2002; 82(2): 124-7.
2. Ohnishi S, Miyagishima T, Nakagawa M, *et al.* Diffuse neonatal hemangiomatosis without cutaneous lesions in an adult—a case report. Angiology 2002; 53(2): 235-7.
3. Frelinghuysen P, Niparko JK. Imaging quiz case 2 [Resident's page: imaging]. Arch Otolaryngol Head Neck Surg 1998; 124(7): 815-8.
4. Hasan Q, Tan ST, Gush J, *et al.* Steroid therapy of a proliferating hemangioma: histochemical and molecular changes [Experience and reason-briefly recorded]. Pediatrics 2000; 105: 117-21.
5. Kushner BJ. Hemangiomas. Arch Ophthalmol 2000; 118 (6): 835-6.
6. Drolet BA, Esterly NB, Frieden IJ. Primary care: hemangiomas in children [Review article]. N Engl J Med 1999; 341(3): 173-81.
7. Marchuk DA. Pathogenesis of hemangioma. J Clin Invest 2001; 107(6): 665-6.
8. Witters I, Van Damme MT, Ramaekers P, *et al.* Benign multiple diffuse neonatal hemangiomatosis after a pregnancy complicated by polyhydramnios and a placental chorioangioma. Eur J Obstet Gyneocol Reprod Biol 2003; 106(1): 83-5.
9. Greinwald JH, Burke DK, Bonthius DJ, *et al.* An update on the treatment of hemangiomas in children with interferon alfa-2a. Arch Otolaryngol Head Neck Surg 1999; 125(1): 21-7.
10. Chang EL, Rubin PA. Bilateral Multifocal hemangiomas of the orbit in the blue rubber bleb nevus syndrome. Ophthalmology 2002; 109(3): 537-41.
11. Von BD, Bieber T, Steen K. Benign neonatal hemangiomatosis in a pre-term infant. J Dermatol 2002; 29(8): 533-5.
12. Hsu RM, Horton KM, Fishman EK. Diffuse cavernous hemangiomatosis of the colon: findings on three-dimensional CT colonography. AJR Am J Roentgenol 2002; 179 (4): 1042-4.
13. Resten A, Maitre S, Humbert M, *et al.* Pulmonary arterial hypertension: thin-section CT predictors of epoprostenol therapy failure. Radiology 2002; 222(3): 782-8.

14. Almagro P, Julia J, Sanjaume M, *et al.* Pulmonary capillary hemangiomatosis associated with primary pulmonary hypertension: report of 2 new cases and review of 35 cases from the literature. Medicine (Baltimore) 2002; 81(6): 417-24.

15. Abramson LP, Gerber S, Chen YH, *et al.* Fetal constrictive pericardial defect with pulmonary capillary hemangiomatosis. J Pediatr Surg 2002; 37(10): 1512-4.

縱膈血管瘤病—病例報告

陳偉仁　鄭高珍　謝俊民　馮瑤*　張晉民**　莊世松***　柯獻欽

血管瘤是良性的血管贅瘤，通常好發於皮膚、皮下組織、口腔及生殖器官的黏膜、以及腹腔內臟。多發性血管瘤被定義為血管瘤病。大部份的血管瘤不需要積極治療，然而基於血管瘤的位置、大小及狀態，約有一成至二成的病例是需要進行治療的。使用放射線學來診斷血管瘤是有困難的，因為血管瘤會表現得類似其他的病灶或腫瘤。除非經由手術，否則通常是無法輕易把血管瘤診斷出來。

我們報告的這個病例是一位18歲患者，主訴有數年的呼吸困難及胸痛。胸部X光片顯示有一縱膈腫瘤，電腦斷層導引的切片報告則為胸腺瘤。然而經由開胸肺切片之後，最終診斷報告確定為縱膈血管瘤病。*(胸腔醫學 2004; 19: 125-131)*

關鍵詞：血管瘤，血管瘤病，胸腺瘤

台南奇美醫學中心　胸腔內科　胸腔外科*　放射科**　病理科***
索取抽印本請聯絡：柯獻欽醫師，奇美醫學中心胸腔內科，台南縣永康市中華路901號

Desquamative Interstitial Pneumonitis — A Case Report and Literature Review

Li-Hui Soh, Cheng-Liang Tsai, Chung-Kan Peng, Chuan-Tsai Lai*, Wann-Cherng Perng, Chin-Pyng Wu, Horng-Chin Yan

Desquamative interstitial pneumonitis (DIP) is a subgroup of interstitial lung disease that has a distinctive histopathology, with macrophages filling the alveolar spaces and no significant fibrosis. DIP has a strong association with cigarette smoking, and a better prognosis and response to corticosteroid. We report a patient with iatrogenic Cushing's syndrome who presented with progressive dyspnea and a bilateral diffuse ground-glass pattern on the chest roentgenograph, and who was diagnosed with DIP after video-assisted thoracoscopic (VATS) lung biopsy. Her condition was uneventful after treatment with corticosteroid. The development of DIP in this case may be associated with cigarette smoking and the abrupt discontinuation of the corticosteroid. ***(Thorac Med 2004; 19: 132-138)***

Key words: DIP, desquamative interstitial pneumonitis, ILD, interstitial lung disease.

Introduction

Desquamative interstitial pneumonitis (DIP) is a term first used by Liebow et al. [2] in 1965 to describe a subgroup of interstitial lung disease with characteristic pigmented macrophages evenly dispersed within alveolar spaces, but without significant fibrosis. It is also currently believed that DIP is related to cigarette smoking. DIP accounts for less than 3% of smoking-related interstitial lung disease [7-8]. Unlike usual interstitial pneumonitis (UIP), DIP has been shown to have a better response to corticosteroid. The 10-year survival rate is about 70%. However, some DIP patients may continue to worsen despite treatment, and late relapse as well as recurrence may occur during treatment [8]. Herein, we report a patient with iatrogenic Cushing's syndrome who presented with progressive dyspnea and a bilateral diffuse interstitial pattern on the chest X-ray. DIP was diagnosed by VATS lung biopsy and responded well to corticosteroid.

Case Report

A 34-year-old female was admitted to our hospital in April 2003, with symptoms of a cough with whitish sputum, fever, and dyspnea for 2 days. She had a history of major depression, and had received regular medical treatment at a medical center for 2 years. She had smoked 2 packs of cigarettes per day for more than 10 years. Four years prior to this admission, she began to suffer from episodes of shortness of breath with a wheezing sound, and was treated for bronchial asthma by physicians from several different hospitals. In addition, she had been taking "pain-killers" and receiving intramuscular

Division of Pulmonary Medicine, Department of Medicine, and *Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China
Address reprint requests to: Dr. Horng-Chin Yan, Division of Pulmonary Medicine, Department of Medicine, Tri-Service General Hospital, Number 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan, R.O.C.

injections at a local clinic for her hip pain in the most recent few months. She stopped all medication when she was hospitalized for a urinary tract infection, one month before this admission.

On this admission, a female with a moon-shaped face, truncal obesity, and abdominal striae, typical of a cushingoid appearance, was observed. The initial vital signs were blood pressure: 158/90 mmHg; body temperature: 36.6℃; pulse rate: 86/min, and respiratory rate: 34/min with intermittent tachypnea. Chest auscultation revealed diffuse expiratory wheezing and inspiratory fine crackles. The hemogram revealed: RBC 4.16 x 10^6/μl, Hb 13.5 g/dl, and WBC 23850 x 10^3/μl, with 90% neutrophils, 7% lymphocytes, 3% monocytes, and 0% eosinophils. Platelet count was 320 x 10^3/μl. Blood chemistry data were within normal limits. CRP was 15.12 mg/dl. The room air arterial blood gas analysis (ABG) revealed: pH 7.434, P_aCO_2 41.5 mmHg, PaO_2 65.2 mmHg, HCO_3^- 27.2 mEq/L, and SaO_2 92.9%. The morning cortisol level was 7.59μg/dL (normal range: 4.3 - 22.4μg/dL / 7-9 AM). Antinuclear antibodies and the rheumatoid factor were negative. The chest roentgenograph revealed a diffuse interstitial pattern (Figure 1A). The patient was medicated with broad-spectrum antibiotics that included 3rd generation cephalosporin, baktar, and macrolide, under the suspicion of severe community-acquired pneumonia (CAP) and possible *Pneumocystis carinii* pneumonia infection. Progressive dyspnea and tachypnea with a respiratory rate around 35/min, tachycardia with a pulse rate of 120/min, and fever up to 38.4℃, were noted the following day. The repeated ABG revealed pH 7.291, $PaCO_2$ 50 mmHg, PaO_2 71.2 mmHg, HCO_3^- 23.3 mEq/L, and SaO_2 93.3% (with FiO_2 60% via a face-tent). The follow-up chest roentgenograph (Figure 1B) showed diffuse increased bilateral opacities. High resolution computed tomography (HRCT) of the chest revealed diffuse bilateral areas of infiltration and ground-glass opacities in a geographic patchy distribution in both lungs. There was no lymphadenopathy or focal mass, but a small amount of pleural effusion in the bilateral lung fields (Figure 2). Since the sputum and blood cultures, as

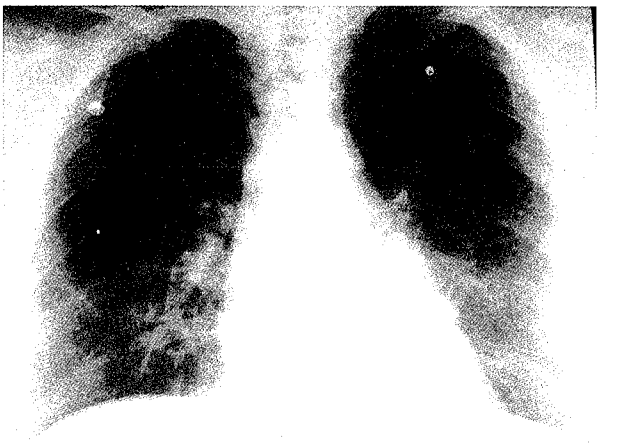

Fig. 1(A). Chest roentgenograph taken at the time of hospital admission, showing
a bilateral diffuse interstitial pattern.

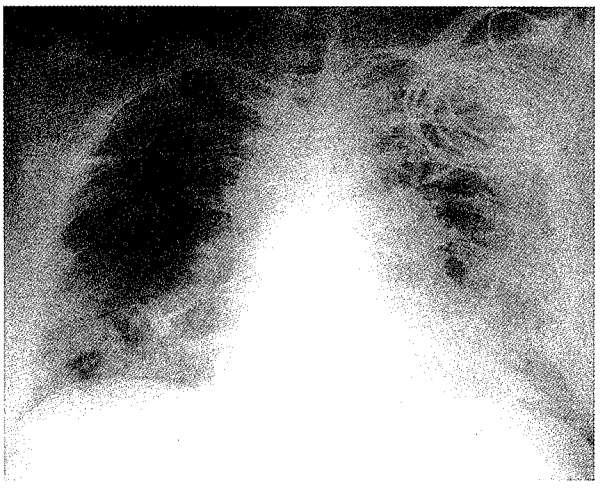

Fig. 1(B). Deterioration of the clinical condition with increased opacities and ground-glass pattern in both lungs.

well as the virology and serology tests for common CAP pathogens, were unrevealing, she underwent a VATS lung biopsy 6 days after admission. The lung biopsy revealed a typical picture of DIP, which showed alveolar spaces filled with foamy histiocytes, and hyperplasia of alveolar type II cells along the alveolar membrane without significant fibrosis (Figure 4A, 4B). Methylprednisolone 40mg q8h was introduced and antibiotics were discontinued simultaneously, as no bacterial or other pathogens were identified. In addition, avascular necrosis of the bila-

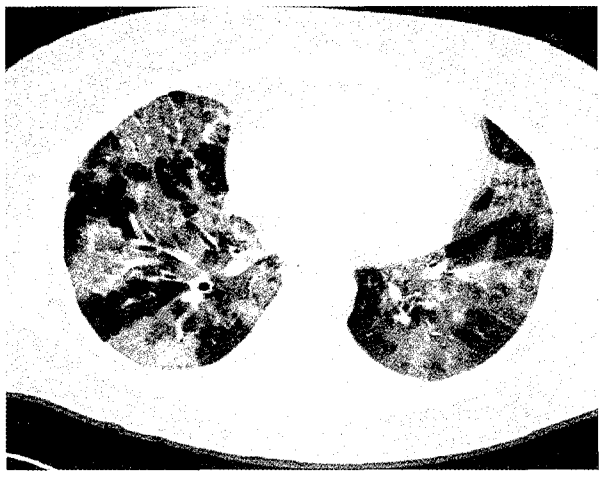

Fig. 2. HRCT reveals ground-glass opacity in a geographic patchy distribution in both lungs. There was no significant fibrosis.

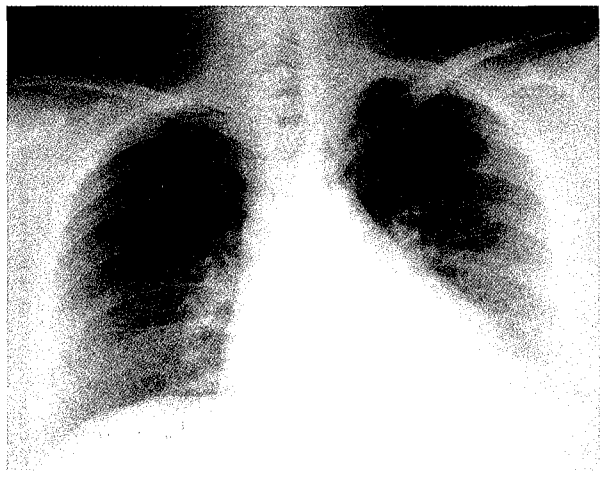

Fig. 3. Chest roentgenograph in resolution was obtained 12 days after steroid therapy.

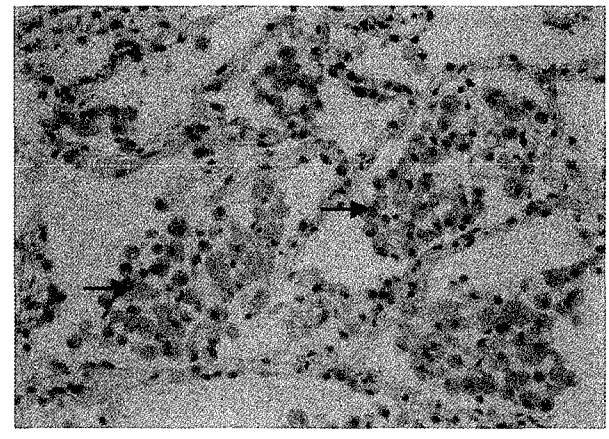

Fig. 4(A). Foamy histiocytes filling in the alveolar spaces and hyperplasia of alveolar type II cells along the alveolar membrane. There was no significant interstitial fibrosis. (H and E stain,200X)

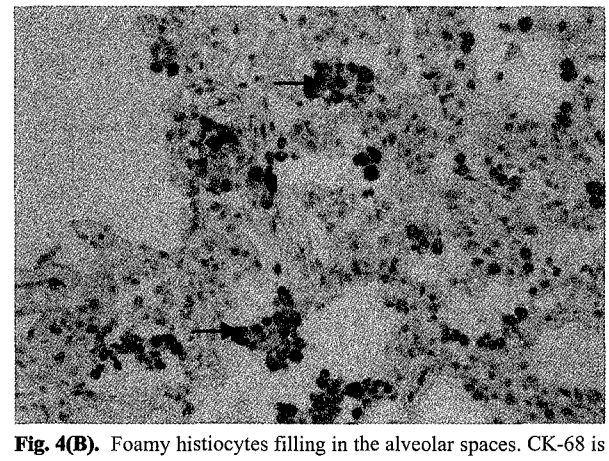

Fig. 4(B). Foamy histiocytes filling in the alveolar spaces. CK-68 is positive (black arrow). (H and E stain, 400X)

teral hip joints was diagnosed. The patient was weaned from the ventilator successfully, without complication. She was discharged 2 weeks after beginning steroid therapy. The follow-up chest roentgenographs revealed a dramatic improvement of the interstitial infiltration (Figure 3). As of this writing, she is being treated with prednisolone, which was tapered from 20mg/day to 10mg/day in the outpatient department.

Discussion

Desquamative interstitial pneumonitis is currently classified as a form of idiopathic interstitial pneumonitis [1]. Liebow et al. and Gaensle et al. were the first to identify the histopathology of DIP, which presents the striking morphological features of: (1) groups of cells in the alveolar spaces, presumably of epithelial origin; (2) an absence of necrosis, a hyaline membrane, and fibrin; (3) minimal or no mural fibrosis; (4) monotonous uniformity; and (5) lymphocyte infiltration [2-3]. Honeycomb change, if present, is minimal. Subsequently, the cells in the alveolar spaces were shown to be macrophages, which were CK68 positive but cytokeratin negative. Furthermore, eosinophils and neutrophils

may be seen within the alveolar spaces [2-5]. However, the histopathological picture is not pathognomonic. Chronic eosinophilic pneumonitis and respiratory bronchiolitis-interstitial lung disease (RB-ILD), for example, may have a similar histopathological picture [4,6]. In RB-ILD, macrophages were shown to fill respiratory bronchioles, adjacent alveolar ducts, and alveoli, the only distinction being the presence of a more diffuse involvement of the airspaces in DIP [4,6].

Whether DIP exists as a distinct disease entity of ILD, or DIP represents the early stage and usual interstitial pneumonitis (UIP) the later stage of the same disease, is still a matter of debate. Some reports have shown that DIP may progress to honeycombing and fibrosis [4]. Currently, DIP is classified as one of the subgroups of interstitial lung disease, which have a better prognosis and response to therapy.

Recent studies have pointed out that cigarette smoking is related to the development of several interstitial lung diseases, including DIP [7-8]. About 90% of DIP patients are former or current smokers, However, DIP accounts for less than 3% of cases of smoking-related ILD. DIP may be seen in association with systemic disorders, infections, or exposures to occupational/enviromental agents and drugs. A "DIP-like" reaction is the term used in this group, and only "idiopathic" cases with no associated disorder are accepted as DIP [7-11]. DIP occurs most commonly in patients 30-50 years of age, and tends to manifest itself at a younger age than does UIP. The incidence ratio between men and women is nearly 2:1. Dyspnea and cough are the most common symptoms, and occur 3 months ~ 5 years before the definite diagnosis is made. Physically, inspiratory crackles are auscultated in 60% of patients. Nearly half of patients have digital clubbing [8].

Radiographically, lung volume is reduced, with a bibasilar, hazy, ground-glass appearance (1/4 of patients) or reticulonodular infiltrates noted. The predominant finding by HRCT is the presence of areas of ground-glass attenuation that may be patchy or diffuse and that mainly affect the middle and lower lobes. Fibrosis is seen in 1/2 of patients; honeycombing, however, is not usually present [12-17]. Areas of ground-glass attenuation in patients with DIP may remain stable or improve with treatment, as discerned by a series of follow-up CT examinations [15]. A restrictive defect with a decreased diffusion capacity is commonly found on the pulmonary function test, but the abnormals are not remarkable [8].

The review by Carrington et al. [8] showed that 21.9% of patients with confirmed DIP had spontaneous improvement even without treatment. However, without treatment, 62.5% of DIP patients had evidence of clinical worsening. With corticosteroid therapy, 61.5% of DIP patients improved as compared to UIP patients (11.5%). Six of the 26 patients in the treated DIP group recovered fully and remained well for 23 years, but 27% of the DIP patients continued to worsen despite treatment. Late relapse as well as recurrence may occur during treatment [8,18-20]. The role of smoking cessation remains unclear [7-8]. A corrected mortality rate for DIP of 30.4%, as compared to 71.5% for UIP patients at the end of 10 years, was shown in the case series of Carrington et al. The average survival was 12 years for DIP patients [8].

In our case, fever, dry cough, progressive dyspnea, and impending respiratory failure were observed. The usual pathogens in atypical pneumonia, including fungal and viral, and parasites such as PCP, could not be ruled out on admission. The possibility of drug-induced lung toxicity was excluded after carefully examining those drugs, including antidepressants, that she had taken during the past few years. The HRCT showed a diffuse ground-glass pattern which correlated with a nonspecific "cellular inflammation" or "active alveolitis". The patient responded well to corticosteroid treatment after open lung biopsy and the diagnosis of DIP had been established. Interestingly, this patient was a heavy smoker and had been taking pain-killers and receiving intramuscular injections for a long time. Due to the difficulty in tracing her medical records, we were unable to obtain a definite cause for the DIP in this case. However, based on the

cushingoid physical features (moon-shaped face, central obesity, abdominal striae, thin skin texture, easy bruising), avascular necrosis of the bilateral hip joints, and depression disorder, iatrogenic Cushing's syndrome was highly suspected in this patient. We believe that the corticosteroid withdrawal before this admission may have been one of the key contributing factors. As DIP responds well to steroids in most cases, however, relapse after tapering off is possible. Fulminant DIP and cases which were refractory to steroid treatment but responded to immunosuppressants have been reported [8,19-20]. The therapeutic effect of steroids may be dose-dependent [21]. Therefore, the development of DIP in this case may be associated with smoking and the abrupt discontinuation of corticosteroid, resulting in a clinical "acute exacerbation".

In conclusion, DIP is an interstitial pneumonitis that responds well to corticosteroid treatment, if a correct diagnosis is made early. Long-term corticosteroid therapy may be needed for some patients with DIP to keep lung inflammation in check (under control). Although the role of smoking cessation in the clinical course of DIP is unclear [7-8], quitting smoking should be encouraged for all DIP patients with a smoking habit.

References

1. American Thoracic Society. American Thoracic Society/ European Thoracic Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002; 165: 277-304.
2. Liebow AA, Steer A, Billingsley JG. Desquamative interstitial pneumonia. Am J Med 1965; 39: 369-404.
3. Gaensler EA, Goff AM, Prowse CM. Desquamative interstitial pneumonia. N Engl J Med 1966; 274: 113-28.
4. Valdivia E, Hensley G, Wu J, *et al.* Morphology and pathogenesis of desquamative interstitial pneumonitis. Thorax 1977; 32: 7-18.
5. Muttun AE, Hasleton PS, Curry A, *et al.* Differentiation of desquamative interstitial pneumonia (DIP) from pulmonary adenocarcinoma. Histopathology 1998; 33: 129-35.
6. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989; 64: 1378-80.
7. Ryu JH, Colby TV, Hartman R, *et al.* Smoking–related interstitial lung disease: a concise review. Eur Respir J 2001; 17: 122-32.
8. Carrington CB, Gaensler EA, Coutu RE, *et al.* Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 1978; 298: 801-9.
9. Bedrossian CM, Kuhn C III, Luna MA, *et al.* Desquamative interstitial pneumonia- like reaction accompanying pulmonary lesions. Chest 1977; 72: 166-9.
10. Lougheed MD, Roos JO, Waddell WR, *et al.* Desquamative interstitial pneumonitis and diffuse alveolar damage in textile workers. Potential role of mycotoxins. Chest 1995; 108: 1196-200.
11. Freed JA, Miller A, Gordon RE. Desquamative interstitial pneumonia associated with chrysotile asbestos fibres. Br J Ind Med 1991; 48: 332-7.
12. Hartman TE, Primack SL, Swensen SJ, *et al.* Desquamative interstitial pneumonia: thin-section CT-findings in 22 patients. Radiology 1993; 187: 787-90.
13. Akira M, Yamamoto S, Hara H, *et al.* Serial computed tomographic evaluation in desquamative interstitial pneumonia. Thorax 1997; 52: 333-7.
14. Heynemen LE, Ward S, Lynch DA, *et al.* Respiratory-bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? AJR 1999; 173: 1617-22.
15. Vedal S, Welsh EV, Miller RR, *et al.* Desquamative interstitial pneumonia. Computed tomographic findings before and after treatment with corticosteroids. Chest 1988; 93: 215-7.
16. Case records of the Massachusetts General Hospital. (Case 40-2002). N Engl J Med 2002; 347: 2149-57.
17. Webb WR, Muller NL, Naidich DP. High-resolution CT of the lung, 3rd ed. Philadephia, PA: LWW; 2001: 384-6.
18. Jeffrey EM, Samuel MA, Jesse R. Idiopathic pulmonary fibrosis: A practical approach for diagnosis and management. Chest 2000; 118: 788-94.
19. Flusser G, Gurman G, Zirkin H, *et al.* Desquamative interstitial penumonitis causing acute respiratory failure, responsive only to immunosuppressants. Respiration 1991; 58: 324-6.

20. Wigger HJ, Berdon WE, Orens CN. Fatal desquamative interstitial pneumonia in an infant: case report with transmission and scanning electron microscopic studies. Arch Pathol lab Med 1977; 101: 129-32.

21. Paul K, Klettke U, Moldenhauer J. Increasing dose of methylprednisolone pulse therapy treats desquamative interstitial pneumonia in a child. Eur Respir J 1999; 14: 1429-32.

脫屑性間質性肺炎—病例報告及文獻回顧

蘇麗慧　蔡鎮良　彭忠衍　賴傳才*　彭萬誠　吳清平　顏鴻欽

脫屑性間質性肺炎（Desquamative interstitial pneumontis）是一種在組織病理學上呈現肺泡填充巨噬細胞且沒有明顯纖維化的間質性肺病。它與抽煙息息相關，且對皮質類固醇治療反應良好。在此我們報告一位醫源性庫辛氏症候群病患臨床表現以漸進性氣促及雙側瀰漫毛玻璃狀肺浸潤的胸部X光表徵，進而以胸腔內視鏡肺切片證實為脫屑性間質性肺炎。此病患對皮質類固醇治療反應良好。此病患之脫屑性間質性肺炎可能起因於抽煙及皮質類固醇的突然終止治療有關。***(胸腔醫學 2004; 19: 132-138)***

關鍵詞：脫屑性間質性肺炎，間質性肺病

國防醫學中心三軍總醫院　內科部　胸腔內科　病理科 *
索取抽印本請聯絡：顏鴻欽醫師，國防醫學中心三軍總醫院胸腔內科，台北市內湖區成功路二段325號

Cardiac Tamponade as a Manifestation of Mycobacterium Avium Complex (MAC) Infection in an Immunocompetent Host — A Case Report

Kuang-Hung Chen, Kwan-Jung Chen, Yueh-Chung Chen*

We present a case of Mycobacterium avium complex (MAC)-induced cardiac tamponade in an immunocompetent man. MAC is ubiquitous and can inhabit the human body without causing disease. Infections with this organism are generally associated with an immunocompromised status, particularly advanced AIDS, as a late opportunistic infection. Sometimes the organism may cause non-tuberculous pulmonary disease in immunocompetent people with preexisting lung disease. Focal extrapulmonary MAC infection in immunocompetent patients is extremely rare, with very few reports in the literature. However, this case serves to remind us that atypical mycobacterial infection must also be considered in immunocompetent patients. ***(Thorac Med 2004; 19: 139-144)***

Key words: mycobacterium avium complex, cardiac tamponade, immunocompetent

Introduction

Mycobacterium avium complex (MAC) is an opportunistic pathogen in acquired immunodeficiency syndrome (AIDS) patients, especially in patients with a CD4 cell count of less than 50 /uL [1]. However, it is an uncommon pathogen in immunocompetent hosts. In the previous literature, most of these cases presented as a non-tuberculous pulmonary disease [2]. Focal extrapulmonary MAC infection is rare, with very few reports in the literature. We report herein a human immunodeficiency virus (HIV)-negative patient with cardiac tamponade induced by MAC infection. This type of case has only been reported once before.

Case Report

A 73-year-old male was admitted to our cardiovascular ward due to the development of progressive shortness of breath and palpitation for 10 days. He had a history of hypertension, which had been under medical control for 10 years. Furthermore, he underwent chest tube drainage for pleural effusion of an unknown cause more than 40 years ago.

On admission, his vital signs were blood pressure 121/51mmHg, pulse rate 98/min, respiratory rate 20/min, and temperature 36.8°C. Physical examination revealed distant heart sounds without murmur. The complete blood count and serum biochemistry studies showed no specific findings. Blood and sputum cultures showed no growth of microorganisms, and the autoantibody series, immunoglobulin, complement level, and urine analysis were normal. The anti-HIV test (ELISA) was non-

Division of Chest Medicine and Division of Cardiovascular Medicine*, Department of Internal Medicine, Jen-Ai Municipal Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Kuang-Hung Chen, Division of Chest Medicine, Department of Internal Medicine, Jen-Ai Municipal Hospital, 10, Section 4, Jen-Ai Road, Taipei, Taiwan

reactive and T-cell lymphocyte subsets were normal. The electrocardiogram showed sinus tachycardia and a reduction of QRS amplitude in the limb leads. Chest radiography showed an enlargement of the cardiac silhouette (Figure 1). The echocardiogram demonstrated a large amount of pericardial effusion with a co-existence of tamponade signs (swinging heart, diastolic collapse of the right ventricle and right atrium, and increased respiratory variation of the mitral inflow).

Immediately following the surgical consultation, thoracotomy for subxiphoid pericardial biopsy was performed, and 500 ml of serosanguineous fluid was drained. The fluid had the following characteristics: glucose 43mg/dL; protein 4.2g/dL; LDH 2285u/L; and WBC 400/cumm with a differential count of 99% mononuclear cells. The Gram stain, silver stain, acid-fast stain, and bacterial culture revealed no organisms. Pathology of the pericardial biopsy showed granulomatous inflammation with a few acid-fast bacilli; no evidence of malignancy was found. Based on these data, mycobacterium-induced pericarditis was strongly suspected. Since the results of the pericardial fluid culture for mycobacterium would not be available for several weeks, anti-tuberculous therapy was initiated with rifampin 600mg/day, isoniazid 400mg/day, pyrazinamide 1250mg/day, and ethambutol 800mg/day.

After this treatment regimen, his dyspnea and palpitation improved markedly, and he was then followed up as an outpatient for 9 days after operation. During the 2-month period of post-operative outpatient follow-up, no clinical, radiological, or ultrasonic evidence of a recurrence of the pericardial effusion was manifested (Figure 2). Two months after discharge, MAC grew in the pericardial fluid culture, and MAC-induced cardiac tamponade was proven. The culture result showed that the MAC was sensitive to rifampin only, and resistant to all other tested anti-tuberculous agents, including iso-

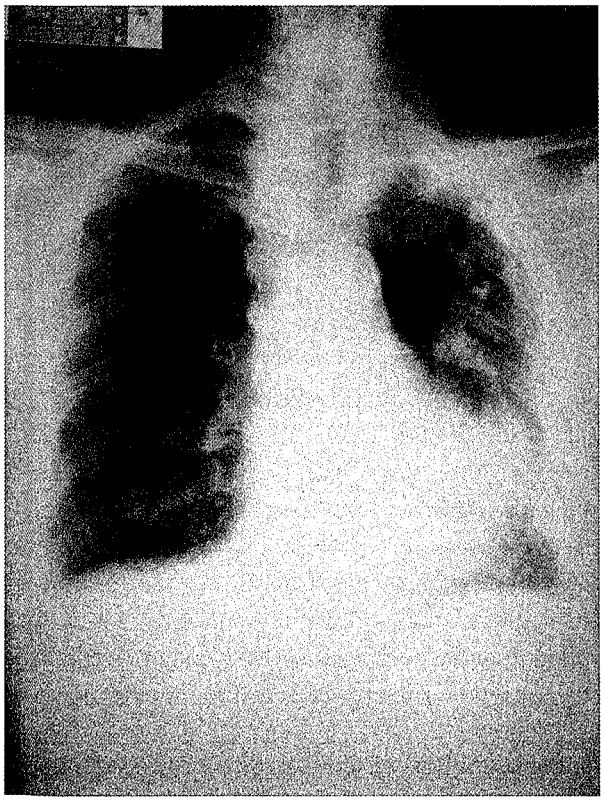

Fig. 1. Chest radiography on admission shows enlargement of the cardiac silhouette.

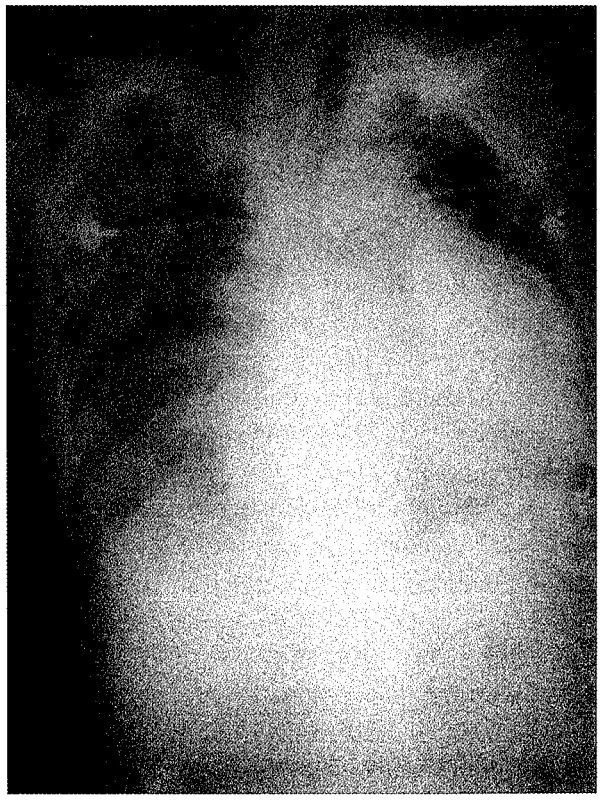

Fig. 2. Chest radiography after operation shows improvement of the cardiomegaly with calcified plaque in the left pleural space.

niazid, ethambutol, p-aminosalicylic acid, streptomycin, kanamycin, and ethionamide.

Discussion

Mycobacterium avium complex is a group of mycobacteria (primarily *M. avium* and *M. intracellulare*) that is ubiquitous, and can be found in water, soil, animals, food products, and other sites [3]. This organism can inhabit the human body surface or organs without causing disease. It can cause two main types of disease in humans. The most common type nowadays is disseminated infection, which occurs in severely immunocompromised patients, such as AIDS patients, as a late opportunistic infection, generally in those with CD4 cell counts less than 50/uL [1,4]. The risk of developing a disseminated MAC infection is inversely correlated with the absolute CD4 lymphocyte count value. In an observational study of AIDS patients, the 1-year incidence for developing MAC bacteremia was 3% for patients with a CD4 count in the 100-199/uL range, and increased progressively to 39% for those patients with a CD4 count <10/uL [1]. Clinical features are usually nonspecific, and include fever, night sweats, weight loss, anemia, fatigue, and diarrhea, which may be incorrectly attributed to a progression of other HIV-related illnesses.

Secondly, in the non-HIV infected population, MAC infection generally presents as a localized infection: a slowly progressive fibrocavitary pulmonary disease in people who usually have pre-existing chronic pulmonary disease [5], or in children with cervical lymphadenitis [3]. In a retrospective study of 513 HIV-negative patients infected with non-tuberculous mycobacteria, only 34 had clinically significant disease. The presentations of mycobacteriosis were found to be lung disease in 23 cases, soft-tissue disease in 10 cases, and disseminated disease in one case. None of the patients presented with pericardial effusion [2].

There is no evidence for person-to-person transmission of MAC, which indicates that MAC is acquired from the environment. The main portals of entry into the body are thought to be the respiratory and gastrointestinal tracts, which are the most common places for MAC colonization in humans [6]. In immunocompetent patients with MAC infection, the lungs usually appear to be the primary site of infection. In HIV-infected patients, however, MAC rarely causes pulmonary disease, but often causes disease in the GI tract, suggesting that the latter route of infection predominates in immunocompromised patients [6]. In this case, the patient was not in an immunocompromised state, and the physical examination and blood culture showed no evidence of disseminated infection; furthermore, the chest radiography and sputum culture showed no evidence of lung infection. No special history or physical examination finding for localized infection, such as neck lymphadenopathy, was found. The infection source and the means of infection remain unknown.

Though MAC-induced disseminated infection frequently involves multiple organs, MAC infection as a cause of pericardial effusion is rare, and has only been described in 5 published cases: 4 patients with AIDS [7-10] and one HIV-negative patient [11]. Corey et al reported a prospective case series of patients with new, large pericardial effusion. A subxiphoid pericardial biopsy and drainage of the pericardial effusion were performed for each patient to determine the etiology. Of the 57 patients, pathogens were identified in eight, including one patient with MAC. This patient with MAC pericardial effusion was non-immunocompromised, and the effusion had resolved unexpectedly by the time of biopsy. The patient had a complete resolution of symptoms after anti-mycobacterial therapy [11].

Diagnosis for MAC infection depends on the type of infection. For disseminated MAC disease, the diagnosis is most readily established by blood culture. Usually one blood culture set will identify more than 90% of patients with MAC bacteremia [12]. Culture of fluid or tissue specimens from suspected sites of involvement may also be considered. For MAC pulmonary disease in HIV-negative patients, the American Thoracic Society has suggested that the diagnosis should be based

on a combination of clinical, radiographic, and microbiologic criteria, including the criterion that the organism should be found in lung secretions more than once, and in large amounts [13]. There are no standard criteria for the diagnosis of focal MAC infection. Our diagnosis for this patient was based on the pathological proof (acid-fast bacilli was found in the biopsy of the pericardium), and the microbiological proof (MAC cultured from the pericardial fluid).

The currently recommended treatment regimen for MAC infection contains at least two drugs, because mono-therapy is associated with the emergence of drug-resistant organisms. MAC is resistant to standard anti-tuberculous drugs, except ethambutol at concentrations achievable in plasma [14]. Proper treatment must include either clarithromycin or azithromycin. Ethambutol is the second-line recommended drug. Rifabutin, ciprofloxacin, or amikacin may be added for people with more severe MAC infections.

In our patient, the pericardial effusion had been successfully controlled by a combination of 4 anti-tuberculous agents, without relapse for 2 months, before MAC infection was confirmed. Yajko reported that at least one half of MAC strains can be inhibited by achievable concentrations of the standard anti-tuberculous agents, although the drug levels necessary to kill MAC *in vitro* (minimum bactericidal concentration) are 8 to 32 times the inhibitory level [15]. In animal models of disseminated MAC infection, both single and combination anti-mycobacterial regimens have reduced mycobacterial colony counts by several logs, and have improved survival [16]. Those reports suggest that if acid-fast bacilli are identified in pericardial fluid, therapy with multiple anti-mycobacterial agents should be initiated prior to bacteriologic confirmation [8]. Because *M. tuberculosis* and MAC both have a similar appearance under the microscope, additional lab tests, including cultures, are required to distinguish them, a process which takes weeks to months. Since MAC infection is relatively rare in immunocompetent humans, and tuberculosis infection is more dangerous both to the patient and to others, we will usually treat for tuberculosis until the culture result is available. The treatment may not lead to a bacteriologic cure for the MAC infection, but it may serve a suppressive role and thus prolong the patient's life [17].

In summary, although MAC is a rare cause of pericardial effusion, especially in immunocompetent patients, the possibility should not be ruled out. Establishing the etiology is important for appropriate therapy. A thorough and systematic evaluation in conjunction with effusion and tissue analysis would be helpful in determining the etiology.

References

1. Nightingale SD, Byrd LT, Southern PM, *et al.* Incidence of Mycobacterium avium-intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 1992; 165: 1082-5
2. Debrunner M, Salfinger M, Brandli O, *et al.* Epidemiology and clinical significance of nontuberculous mycobacteria in patients negative for human immunodeficiency virus in Switzerland. Clin Infect Dis 1992; 15: 330-45.
3. Wolinsky E. Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis 1979; 119: 107-59.
4. Crowe SM, Carlin JB, Stewart KI, *et al.* Predictive value of CD4 lymphocyte numbers for the development of opportunistic infections and malignancies in HIV-infected persons. J Acquir Immune Defic Syndr 1991; 4: 770.
5. Prince DS, Peterson DD, Steiner RM, *et al.* Infection with Mycobacterium avium complex in patients without predisposing conditions. N Engl J Med 1989; 321: 863-8.
6. Jacobson MA, Hopewell PC, Yajko DM, *et al.* Natural history of disseminated Mycobacterium avium complex in AIDS. J infect Dis 1991; 164: 994-8.
7. Choo PS, McCormack JG. Mycobacterium avium: a potentially treatable cause of pericardial effusions. J infect 1995; 30: 55-8.
8. Woods GL, Goldsmith JC. Fatal pericarditis due to Mycobacterium avium intracellulare in acquired immunodeficiency syndrome. Chest 1989; 95: 133-57.
9. Cohen IS, Anderson DW, Virmani RV, *et al.* Congestive cardiomyopathy in association with acquired immunodeficiency syndrome. N Engl J Med 1986; 315: 628-30.
10. Kerns E, Benson C, Spear J, *et al.* Pericardial disease in

patients with HIV infection [Abstract]. 31st Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington DC, American Society for Microbiology 1991; 191.

11. Corey GR, Campbell PT, Trigt PV, *et al.* Etiology of large pericardial effusion. Am J Med 1993; 95: 209-13.
12. Yagupsky P, Menegus MA. Cumulative positivity rates of multiple blood cultures for Mycobacterium avium-intracellular and Cryptococcus neoformans in patients with the acquired immunodeficiency syndrome. Arch Pathol Lab Med 1990; 114: 923-5.
13. American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 1997; 156: S1-25.
14. Kemper CA, Havlir D, Haghighat D, *et al.* The individual microbiologic effect of three antimycobacterial agents, clofazimine, ethambutol, and rifampin, on MAC bacteremia in patients with AIDS. J Infect Dis 1994; 170: 157-64.
15. Yajko DM, Nassos PS, Hadley WK. Therapeutic implications of inhibitions versus killing of Mycobacterium avium complex by antimicrobial agents. Antimicrob Agents Chemother 1987; 31: 117-20.
16. Inderlied CB, Kolonoski PT, Wu M, *et al.* Amikacin, ciprofloxacin, and imipenem treatment for disseminated Mycobacterium avium complex infection of beige mice. Antimicrob Agents Chemother 1989; 33: 176-80.
17. Young LS. Mycobacterium avium complex infection. J Infect Dis 1988; 157: 863-7.

禽型分枝桿菌群(MAC)致心包積水—病例報告

陳光宏　陳寬榮　陳鉞忠*

禽型分枝桿菌群(MAC)是一種環境中常可發現的菌種。它可生長於正常人體的表皮及器官而不致病。此菌種造成感染一般是發生在後天免疫不全的病人身上，尤其當 CD4 細胞數掉到 50/ul 以下時，此時病人的抵抗力極弱，容易形成機會感染。而免疫力正常的人偶有感染，大多發生於肺部有宿疾的病人，而感染部位多在肺部。肺外局部性 MAC 感染在免疫力正常的人極為少見。我們報告一個 73 歲男性，因為 MAC 感染引起心包積水，其 HIV 檢驗結果為陰性。經外科手術引流心包積水並送檢培養的結果證實為 MAC 感染。*(胸腔醫學 2004; 19: 139-144)*

關鍵詞：禽型分枝桿菌群 (MAC)，心包積水，非免疫不全

台北市立仁愛醫院　胸腔內科　心臟內科 *
索取抽印本請聯絡：陳光宏醫師，台北市立仁愛醫院胸腔內科，台北市仁愛路 4 段 10 號

Tuberous Sclerosis with Recurrent Pneumothoraces and Lung Transplantation — A Case Report

Chia-Cheng Tseng, Chao-Chien Wu, Meng-Chih Lin, Ming-Jang Hsieh*

Tuberous sclerosis with lung involvement is very rare. We report herein a case of tuberous sclerosis with recurrent spontaneous pneumothraces, for which lung transplantation was ultimately performed due to refractory cor pulmonale. A 23- year-old woman with tuberous sclerosis presented with recurrent pneumothoraces at our hospital. She had had a past history of right renal angiomyolipoma, and since childhood, she had been noted to have skin lesions with angiofibromas on both cheeks and in the lumbosacral area. With the assistance of sonography, she was also found to have hepatic tumors that had not grown for several years, indicating they were benign. These findings confirmed our diagnosis of tuberous sclerosis. As the disease progressed, chest radiographs revealed more interstitial lung infiltration and honeycombing change. Her pulmonary function also deteriorated progressively. Chronic respiratory failure began in 1999. Although she underwent lung transplantation, she died one year later due to severe infection and malignant lymphomas.

To date, no one has reported an effective treatment for tuberous sclerosis. Although oophorectomy and treatment with progestational agents have been reported to provide improvement or stabilization of the disease in a subset of patients, only lung transplantation, which is an option for some patients, offers the possibility for cure. ***(Thorac Med 2004; 19: 145-151)***

Key words: tuberous sclerosis, recurrent pneumothoraces, lung transplantation, lymphagioleiomyomatosis

Introduction

Tuberous sclerosis is a systemic disease with a clinical triad of mental retardation, epilepsy, and dermal angiofibroma (adenoma sebaceum). Systemic manifestations include calcified cerebral and paraventricular harmatomas, renal angiolipomas, cardiac rhabdomyomas, and periungual fibromas [1]. Patients with this multi-system disease most commonly present with skin lesions and benign tumors of the central nervous system. Renal involvement is common, with angiomyolipomas, usually bilateral, being the most frequent abnormality. Renal cysts, which may also be present, can give an appearance similar to that of autosomal dominant polycystic kidney disease [2]. Heart rhabdomyomas, probably hamartomatous growths, occur in multiples in 90% of the cases. Mortality with cardiac abnormalities is usually due to intramural rhabdomyomas, which affect 30% of individuals

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Division of Thoracic Surgery*, Department of Surgery, Chang Gung Memorial Hospital, Kaohsiung, Taiwan
Address reprint requests to: Dr. Chao-Chien Wu, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, No.123, Ta-Pei Road, Niao-Sung Hsiang, Kaohsiung Hsien, Taiwan

with tuberous sclerosis, resulting in death during the first year of life [3]. Patients inheriting the tuberous sclerosis gene are at an increased risk of developing ependymomas and childhood astrocytomas, more than 90% of which are sub-ependymal giant cell astrocytomas. These are benign neoplasms that may develop in the retina or along the border of the lateral ventricles, and may obstruct the foramen of Monro and produce hydrocephalus [4]. Death, usually from neurologic complications, occurs in more than 75% of affected individuals by age 20.

Tuberous sclerosis involving the lungs is pathologically identical to lymphangioleiomyomatosis (LAM) and, therefore, presents a similar clinical, radiographic, and physiologic picture. However, pulmonary disease is rare, appearing in 1% and only in female patients who survive to adulthood. The onset of dyspnea usually occurs during the third decade. As in LAM, progressive dyspnea, recurrent spontaneous pneumothoraces, and hemoptysis are to be expected. Herein, we present a 23-year-old patient with recurrent spontaneous pneumothoraces who was finally diagnosed as having tuberous sclerosis.

Case Report

In June 1990, a 23-year-old Taiwanese woman visited our emergency room. She complained of right chest pain that suddenly began at 5 a.m. The pain was sharp and worsened if she breathed deeply. A raised erythematous facial rash was noted on examination. She was afebrile, normotensive, and had a normal peripheral pulse. A percussion examination of her chest revealed decreased breathing sounds and hyper-resonance in the right lung field. The chest radiograph revealed pneumothorax in the right lung (Figure. 1). She first underwent tube thoracostomy, and then later was admitted to our chest ward.

Tracing her history, we found that she had experienced two episodes of pneumothoraces, one in the right lung in 1986, and the other in the left lung in February 1990. At that time, she had right flank pain. When searching for the source of that pain, we found a huge right renal tumor, which was removed with a right nephrectomy in January 1990. Pathology revealed an angiomyolipoma, 3.2 kg in weight.

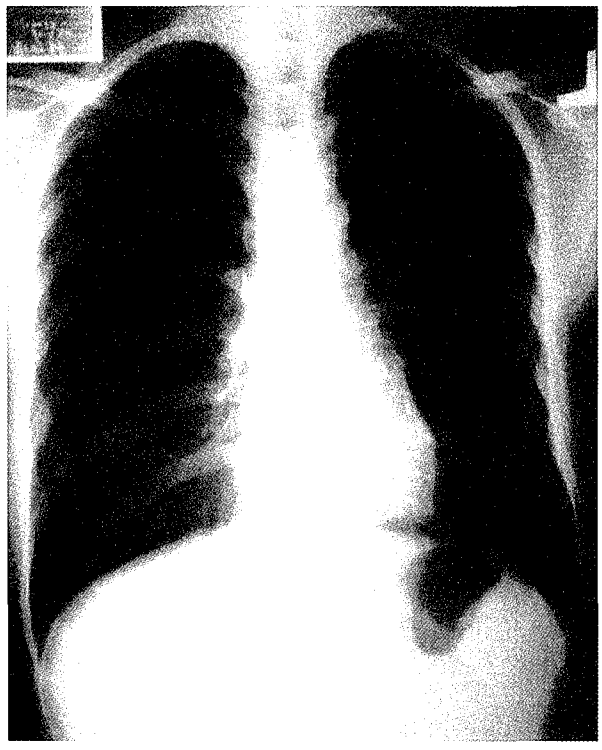

Fig. 1. Chest radiograph reveals pneumothorax in the right lung with mild interstitial infiltration in the bilateral lower lung field.

The patient presented a sporadic case with no family history of the disease. She had normal development of intelligence and no history of seizures. No history of trauma or medical history could add any more to our clinical findings.

Since childhood she had been noted to have skin lesions with erythematous papules on both cheeks and leaf-shaped plaque on the skin of her buttocks. A biopsy of the skin lesions revealed angiofibroma. The patient's presumptive diagnosis was tuberous sclerosis, based on the findings of facial angiofibroma, renal angiomyolipoma, and recurrent spontaneous pneumothoraces. These findings were compatible with Gomez's inclusion criteria for tuberous sclerosis.

At admission, surgery was indicated to treat the

recurrent spontaneous pneumothoraces. During the operation, she was found to have numerous generalized blebs and spots with pigmentation throughout the lung. Pathology reported harmatomatous proliferation. Sonographic findings also revealed her liver to have multiple hyperechogenic lesions, compatible with vascular tumors. These liver lesions had been found much earlier and were followed up by sonography 6 and 9 years after they were first discovered, but no increase in size was noted, strongly suggesting that they were benign.

However, another episode of left spontaneous pneumothorax occurred in December 1990. A left thoracotomy with repair of air leaking blebs and pleurodesis were both performed.

After discharge, the patient seemed quite well and had no specific complaint related to lung disease. A pulmonary function test that was done at that time showed FVC to be 70% and FEV_1 to be normal, which meant she could be considered as having only a mild restrictive ventilatory impairment. In June 1995, she complained of dyspnea on exertion and occasional hemoptysis episodes. She was observed to have wheezing and moderate obstructive ventilatory impairment. She was prescribed a bronchodilator and inhaled corticosteroid. Polyvalent pneumococcal vaccine and annual influenza vaccinations were also given. With these medications, the patient could initially tolerate her symptoms, but, starting in April 1997, she experienced more profound dyspnea on exertion and hemoptysis. She was found by spirometry to have moderate to severe obstructive and restrictive ventilatory impairment.

Over time, her condition deteriorated. PFT showed severe obstructive ventilatory impairment and a resting oxygen saturation below 90%, so she began receiving oxygen therapy in January 1999. The chest radiograph and computed tomography (CT) showed more interstitial lung infiltrations and honeycombing lesions than she had had nine years before (Figure 2, 3). Anti-estrogen therapy with tamoxifen had been tried for one month in 1999, to no benefit.

Despite all efforts, medical management of her symptoms was failing and her condition deteriorated rapidly. She underwent a lung transplantation due to chronic respiratory failure in June 2001.

Although she received regular immunosup-

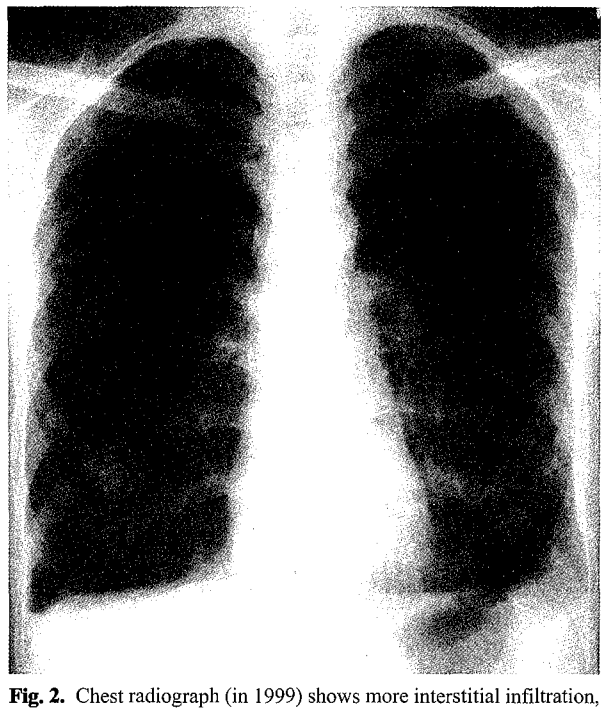

Fig. 2. Chest radiograph (in 1999) shows more interstitial infiltration, honeycomb lesions, and hyperinflation compared to that of Figure 1 (in 1990); bilateral pleural thickness is also noted.

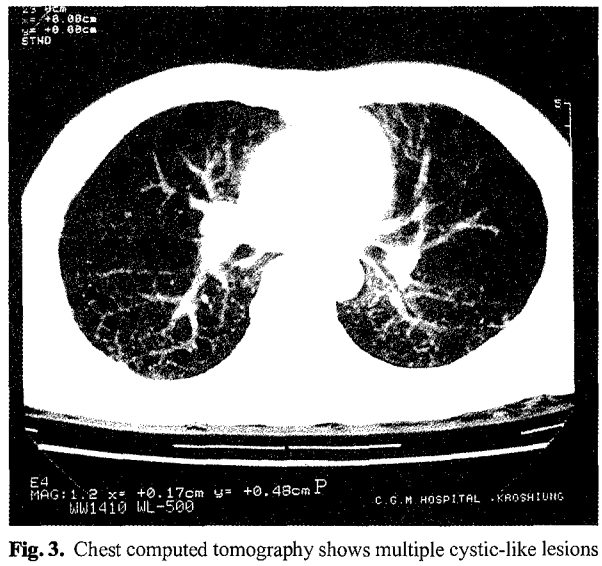

Fig. 3. Chest computed tomography shows multiple cystic-like lesions permeating the entire lung parenchyma.

pressant medication after lung transplantation, the continuing dyspnea negatively affected her quality of life, especially when she came down with a common cold. One year after lung transplantation, the patient died due to severe infection and malignant lymphomas.

Discussion

Tuberous sclerosis (Bourneville's disease) is a rare autosomal dominant disorder, with a prevalence varying from 1/27,000 to 1/100,000 population. Family history may be negative, and it is estimated that up to 68% of cases is caused by new mutations [5]. There are distinctive differences in age, sex, and presenting symptoms in tuberous sclerosis patients with lung involvement and those without (Table 1).

Kidney involvement, especially cysts and angiomyolipomas, is common. Renal angiomyolipomas have been reported to be one of the most important extrapulmonary complications of tuberous sclerosis, and often occur multiply and bilaterally. They are reported in up to 60% of the patients with LAM [6]. Massive bleeding, a major complication of renal angiomyolipomas [6-8], may cause symptoms of shock. In mild cases, angiomyolipomas result in intratumoral hemorrhage or cause chronic flank pain.

Although the association of tuberous sclerosis and renal angiomyolipomas is well established, the occurrence of hepatic benign tumors in this disease is less well documented. Pathologically, intrahepatic angiomyolipomas, lipomas, and hemangiomas have been reported. Until now, approximately 100 cases of hepatic counterparts have been reported since they were first described by Ishak in 1976, though hepatic angiomyolipomas do not necessarily always occur with tuberous sclerosis [9-10]. Multiple hepatic angiomyolipomas are extremely rare. Only six cases have been reported, and most of them (5/6) have been associated with tuberous sclerosis [9].

The pulmonary manifestations of tuberous sclerosis are indistinguishable from those of LAM. The onset of lung involvement generally occurs during the third to fourth decade of life; it rarely occurs before age 20. When pulmonary involvement is present, there is a marked female predominance, especially in those of childbearing age [11], though the complete clinical triad described is rarely found. Most patients with lung involvement will present dyspnea, but about one-third will have the onset of the disease marked by recurrent spontaneous pneumothoraces [12]. Hemoptysis and chest pain are also important clinical features, but chylothorax is rare [13]. The dyspnea is usually progressive, leading to respiratory failure, and cor pulmonale, which may be fatal. The rapidity of progression of this airflow obstruction is highly variable among patients.

Possible radiographic findings of tuberous sclerosis include interstitial opacities, honeycomb changes, and hyperinflation, although the radiograph may be normal early in the course of the disease [14]. As the disease progresses, cysts enlarge, ranging in diameter from a few millimeters to several centimeters, and may coalesce, causing architectural distortion. Thin-section CT is superior to plain radiography, and often reveals cysts in the lung parenchyma even when the chest radiographic finding is normal at the early stage [7,14-5]. Although these findings are very useful in establishing the diagnosis of LAM, they are not pathognomonic of

Table 1. Comparison of tuberous sclerosis with and without lung involvement.

Features	Without lung involvement	With lung involvement
Age at onset	<20 years old	20-35 years old
Presenting symptoms	CNS disorder	Dyspnea
Male: Female	1:1	1:5
Mental retardation (%)	60%	40%
Epilepsy (%)	80%	20%

the disease. Similar cysts can be seen, for instance, in Langerhans' cell histiocytosis and emphysema. It is desirable to perform a lung biopsy for histologic confirmation of the diagnosis. Pulmonary function studies often reveal evidence of gas trapping and demonstrate obstruction to airflow and reduced single breath diffusing capacity, but otherwise, spirometric indexes are normal.

Pulmonary tuberous sclerosis or LAM is characterized by a hamartomatous proliferation of smooth muscles in the walls of the airways, venules, and lymph vessels in the lung. The involvement of airways results in narrowing, obstruction, and air trapping. Damaged alveoli coalesce, eventually leading to a cystic formation, which may rupture, resulting in pneumothorax [15]. Obstruction of the venous flow in the lung results in venous distension, pulmonary venous hypertension, and hemoptysis. Lymphatic obstruction leads to chylothorax, a complication that appears more commonly in LAM than in tuberous sclerosis. Infradiaphragmatic lymphatic obstruction may result in retroperitoneal cystic masses [15].

Airway obstruction is managed with a bronchodilator. Pneumothorax is managed in the usual way, with the insertion of a chest tube. As pneumothoraces may be recurrent, mechanical or chemical pleurodesis may be necessary; however, these procedures do not rule out future lung transplantation.

Because of the disease's similarity to LAM, which is thought to be brought about in part by female hormones, hormonal manipulation provides the mainstay of treatment [16]. Progesterone, tamoxifen, luteinizing hormone-releasing hormone (LHRH) analogs, and/or oophorectomy, have been used in the treatment of women. Only oophorectomy and treatment with progestational agents, however, have appeared to provide a reliable improvement or stabilization of the disease in a subset of patients [7, 16]. As the disease progresses to the stage of respiratory failure, lung transplantation may offer the only hope for cure. In a retrospective study of 34 cases of lung transplantation for pulmonary LAM, the survival rate was 69% at one year and 58% at 2 years, similar to the post-transplant figures for other lung diseases [16]. The main causes of post-lung transplant death are acute lung injury (early stage), and infection and bronchiolitis obliterans (late stage). Post-transplant lymphoproliferative disorders associated with Epstein-Barr virus occur in 5 to 10% of lung transplant recipients. Nearly all occur within the first year after transplant. Recent data suggest a much higher incidence of this disease in patients who are Epstein-Barr naive and who receive an Epstein-Barr positive graft. Treatment for this disorder, reported to have an approximate 50% survival rate, is usually reduced immunosuppression and antiviral and anti-B lymphocyte drugs. Survivors often develop bronchiolitis obliterans [17].

Patients with tuberous sclerosis have a decreased survival compared to the general population. Renal disease and brain tumors are the most common causes of death [5]. Pulmonary involvement in tuberous sclerosis carries a poor prognosis, with progressive disease being common. Death secondary to respiratory failure often occurs within five years of the onset of symptoms. However, survival time up to 20 years in some cases has been described. In our report, the patient survived 11 years after the symptoms began. The most recent studies report a 10-year survival rate of around 70% to 79% [6]. Long-term survival may occur more frequently today because of improved management for potential complications, especially cor pulmonale and pneumothoraces.

References

1. Schwarz MI, Cherniack RM, King TE. Diffuse alveolar hemorrhage and other rare infiltrative disorders. Murry JF, Nadel JA, Mason RJ, *et al.* Textbook of Respiratory Medicine, 3rd ed, Philadelphia, W.B. Saunders Company, 2000, 1733-55.
2. Asplin JR, Coe FL. Hereditary tubular disorders. Braunwald E, Fauci AS, Kasper DL, *et al.* Harrison's Principles of Internal Medicine, 15th ed, New York, McGraw-Hill Companies, 2001, 1598-606.
3. Damm DD, Tomich CE, White DK, *et al.* Intraosseous fibrous lesions of the jaws. Oral Surgery Oral Pathology

Oral Radiologic Endodontology 1999; 87: 337-40

4. Sagar SM, Israel MA. Primary and metastatic tumors of the nervous system. Braunwald E, Fauci AS, Kasper DL, *et al.* Harrison's Principles of Internal Medicine, 15th ed, New York, McGraw-Hill Companies, 2001, 2442-52.
5. King TE, Crausman RS. I. Pulmonary involvement in tuberous sclerosis. II. Pulmonary lymphangioleimyomatosis. In: UpToDate, Rose, BD (Ed), UpToDate, Wellesley, MA, 2003.
6. Rebacca A, Pauw D, Johan R, *et al.* Renal angiomyolipoma in association with pulmonary lymphangioleiomyomatosis. American Journal of Kidney Diseases 2003; 41: 877-83.
7. Chu SC, Horiba K, Usuki J, *et al.* Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999; 115: 1041-52.
8. Lindsey A.K, Michael L.B, Ryu JH, *et al.* Renal Angiomyolipoma in association with pulmonary lymphangioleiomyomatosis: forme fruste of tuberous sclerosis. Urology 1993; 41: 440-4.
9. Kim RE, Chung MP, Park CK, *et al.* Pulmonary lymphangioleiomyomatosis and multiple hepatic angiomyolipomas in a man. Pathology International 2003; 53: 231-5.
10. Carmody E, Yeung E. McLoughlin M. Angiomyolipomas of the liver in tuberous sclerosis. Abdominal Imaging 1994; 19: 537-9.
11. Costello LC, Harman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis. Mayo Clin Proc 2000; 75: 591-4.
12. Kyriss T, Eulenbruch H, Friedel G, *et al.* Secondary spontaneous pneumothoroax in tuberous sclerosis. Der Chirurg 2001; 72: 1504-7.
13. Foresti V, Casati O, Zubani R, *et al.* Chylous pleural effusion in tuberous sclerosis. Respiration 1990; 57: 398-401.
14. McCormack F, Brody A, Meyer C, *et al.* Pulmonary cysts consistent with lymphangioleiomyomatosis are common in women with tuberous sclerosis. Chest 2002; 121: 61S.
15. Halabi S, Convery R, Curtis JM. Progressive dyspnea in a 49-year-old woman with long standing epilepsy. Chest 2002; 122: 352-5.
16. Logginidou H, Ao X, Russo I, *et al.* Frequent estrogen and progesterone receptor immunoreactivity in renal angiomyolipomas from women with pulmonary lymphangioleiomyomatosis. Chest 2000; 117: 25-30.
17. Maurer JR. Lung transplantation. Braunwald E, Fauci AS, Kasper DL, *et al.* Harrison's Principles of Internal Medicine, 15th ed, New York, McGraw-Hill Companies, 2001, 1531-4.

結節性硬化症合併反覆性氣胸及肺移植—一個案例報告

曾嘉成　吳沼澦　林孟志　謝敏暲*

結節性硬化症合併肺部侵犯是非常罕見的。在這裡我們報導一個反覆性自發性氣胸的案例，最後發生肺心症且內科藥物治療無效而實施肺臟移植。這一個結節性硬化症的23歲女性病患，以反覆性自發性氣胸為其初始症狀，她有右腎血管肌肉脂肪瘤的過去病史，在兩臉頰及腰臀部的皮膚病灶發現血管纖維瘤，皮膚病灶在孩提時即存在。在超音波檢查下也發現肝臟腫瘤且數年之後腫瘤皆無變大的趨向，應是良性腫瘤；這些發現肯定結節性硬化症的診斷。隨著疾病的進展，胸部X光發現更多的間質性浸潤及蜂窩狀的改變，肺功能也逐漸阻塞並惡化，慢性呼吸衰竭及肺心症在十年後發生，肺臟移植在內科藥物治療失效後實施，但病患依然在肺移植一年後因嚴重感染及惡性淋巴瘤死亡。

到今天為止，對於結節性硬化症依然沒有比較有效的治療方法，雖然卵巢切除術及黃體素劑在一些病人身上看到療效，但只有肺臟移植，在一些肺部嚴重侵犯的病人上，是唯一可以治療痊癒的選擇。*(胸腔醫學 2004; 19: 145-151)*

關鍵詞：結節性硬化症，自發性氣胸，肺臟移植，淋巴管平滑肌增生症

高雄長庚紀念醫院　胸腔內科　胸腔外科 *
索取抽印本請聯絡：吳沼澦醫師，高雄長庚紀念醫院胸腔內科，高雄縣鳥松鄉大埤路 123 號

Fibrous Dysplasia with Malignant Transformation of the Rib — A Case Report

Nai-Chuan Chien, Chen-Tu Wu*, Yung-Chie Lee

Fibrous dysplasia is probably the result of an aberration in the development of the bone. Malignant transformation is rare and has been estimated in less than 1% of the cases. We report a case of fibrous dysplasia with osteogenic sarcoma transformation of the second rib. The patient was treated by a wide resection of the rib. Adjuvant radiotherapy was performed at another hospital. There was no sign of recurrence 2 years after operation. ***(Thorac Med 2004; 19: 152-156)***

Key words: fibrous dysplasia, osteogenic sarcoma

Introduction

Fibrous dysplasia of the bone is a benign lesion characterized by a proliferation of fibroconnective tissue associated with a metaplastic formation of immature non-lamellar bone. It has been generally considered a developmental disorder. Malignant transformation is rare and has been estimated to occur in less than 1% of cases [1]. We report a case of fibrous dysplasia with osteogenic sarcoma transformation of the second rib, and discuss the etiology, clinical presentation, pathological findings, and treatment of the disease.

Case Report

A 39-year-old man suffered from high fever, chills, and bilateral flank pain in December 2000. Under the impression of acute pyelonephritis, he was admitted to a local hospital. A firm, fixed, oval shape tumor measuring 7.0 cm x 5.0 cm was palpated on the right anterior chest wall incidentally during admission. He was transferred to our hospital on Dec. 23, 2000. There were no symptoms or signs of chest pain or café au lait pigmentation. The patient was a shoemaker and worked in a factory. Organic solvent exposure was documented, but there was no radiation exposure. Hemoglobin, white cell count, alkaline phosphatase, calcium, phosphorus and C-reactive protein tests showed normal results.

The chest roentgenogram showed an expansile lesion with a lacy appearance in the right second rib (Figure 1). A computerized tomogram of the chest revealed an expansile mass with a low-density area suspected of having cortical destruction at the anterior part (Figure 2). A bone scan showed increased uptake only over the lesion in the right second rib.

The tumor was removed *en bloc*. Postoperative adjuvant radiotherapy with 5000 cGy was performed at another hospital. The patient has been well for 2 years after the surgery.

Division of Chest Surgery, Department of Surgery, Department of Pathology*, National Taiwan University Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Nai-Chuan Chien, Department of Surgery National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan

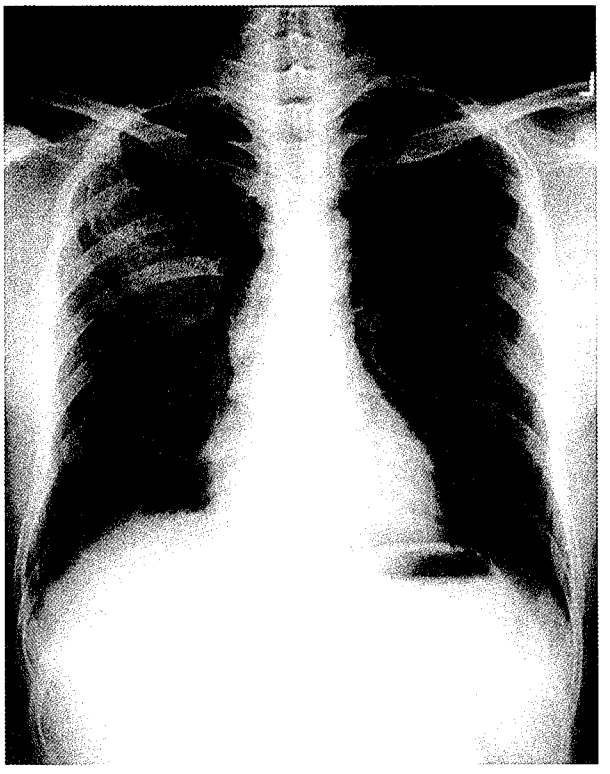

Fig. 1. Radiography of the right second rib. The tumor is expansile with a lacy appearance.

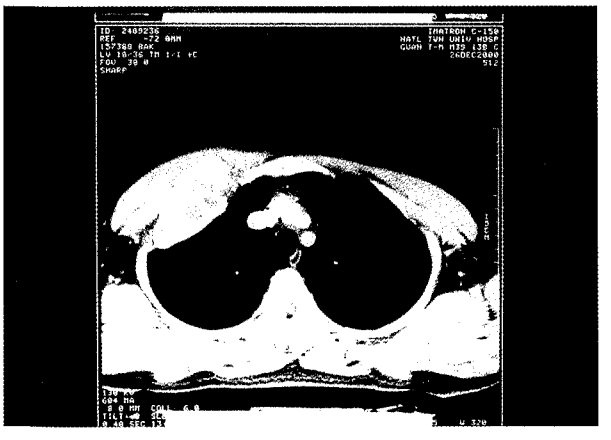

Fig. 2. Computed tomogram of the lesion shows focal low densities at the anterior portion suspected of being cortical destruction.

Pathological Findings

The specimen submitted consisted of a bulging mass with two short segments of rib tissue at either end. Grossly, the tumor was well demarcated, measuring 8.0 x 6.0 x 6.0 cm in size. On cutting, the tumor was gray-white and not gritty in texture. There were a few cysts measuring up to 2.0 x 1.0 x 1.0 cm surrounded by relatively gray-brown soft tumor tissue. A thin shell of the cortical bone was seen on the whole tumor, although the focally bulging cortex could also be seen. There was no extension of the soft tissue (Figure 3).

Microscopically, most of the tumor tissue was rather typical of fibrous dysplasia with a proliferation of stromal cells in dense collagenous matrix. The stromal cells in this area had no cytologic atypia. A prominent component within the matrix was the presence of small, odd-shaped trabeculae of woven bone without osteoblastic rimming (Figure 4). However, several small foci of hypercellularity, corresponding grossly to the gray-brown and soft areas, were evident. In these foci, some of the small osteoid or woven bone trabeculae were necrotic with osteoclastic resorption and leukocyte infiltration. The nuclei of stromal cells in these foci showed hyperchromatism and a variation in nuclear size and shape. Numerous mitotic figures were present (Figure 5). This was suggestive of malignant transformation of an osteogenic nature.

Discussion

Malignant transformation in fibrous dysplasia

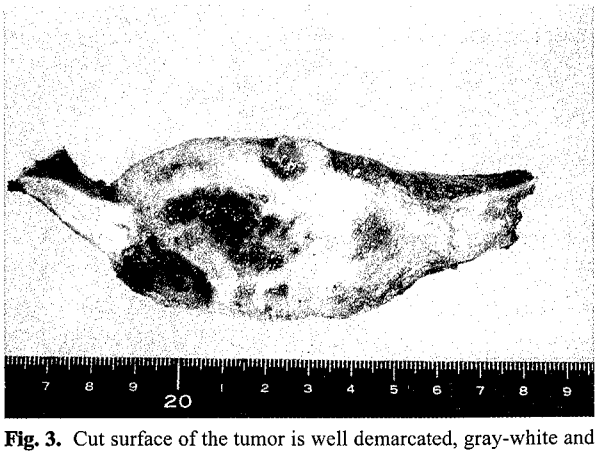

Fig. 3. Cut surface of the tumor is well demarcated, gray-white and not gritty on cutting with foci of gray-brown and soft tumor tissue surrounding a few small cysts. The cortex, though thin and focally bulging, is well preserved.

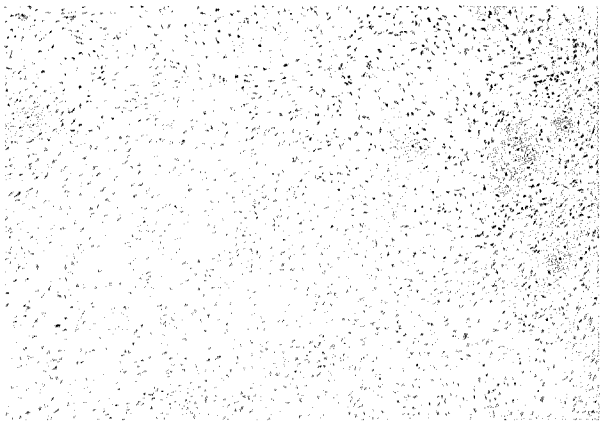

Fig. 4. Typical histological appearance of fibrous dysplasia characterized with odd-shaped woven bone trabeculae, without osteoblastic rimming, dispersed in a collagenous background containing proliferating stromal cells is composing the main area of the tumor. (H&E, Original magnification 33X)

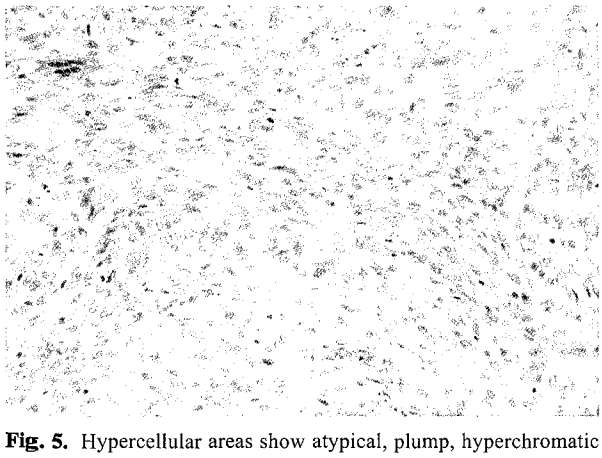

Fig. 5. Hypercellular areas show atypical, plump, hyperchromatic stromal cells with increased mitotic activity. (H&E, Original magnification 66X)

is rare and the incidence varies from 0.4% to 6.7% [2-3]. The first case was reported in 1945 [4]. It has been suggested that malignant change is more likely to occur in polyostotic than monostotic forms. The most common histological type is osteosarcoma, followed by fibrosarcoma and chondrosarcoma [5,11].

The treatment of fibrous dysplasia by radiation has an increased probability for malignant transformation to osteosarcoma. Ruggieri and coauthors reported on 28 cases of sarcomas in 1,122 examples of fibrous dysplasia from the Mayo Clinic file. Thirteen of the patients had received radiation [5]. In another report, the authors concluded that radiotherapy is not the treatment of choice for fibrous dysplasia therefore [3]. There has been no report regarding organic solvent and malignant transformation in fibrous dysplasia. The radiological and pathological features in this case would indicate that locally aggressive behavior, as well as high-grade malignant change, can occur concurrently in fibrous dysplasia. Those patients with an adequate operation and adjuvant chemotherapy seem to do better [5]. The prognosis is similar to that of other malignancies without fibrous dysplasia [5-6]. Yabut et al reported that most patients died with pulmonary metastasis, and the mean survival period was 3-4 years [3]. There are no larger series with a comparison of prognoses in several different control groups presented in the literature. Since the modalities of treatment for osteosarcomas has greatly improved the prognosis recently, the treatment of choice for this kind of patient, currently, may be different, and need further investigation.

Fibrous dysplasia of the bone has long been considered a developmental disorder. However, several cytogenetic investigations since 1989 have revealed features of clonal proliferation with chromosomal aberrations in fibrous dysplasia [7]. Dal Cin et al concluded that fibrous dysplasia is a neoplastic disease associated with genetic lesions in chromosomes 2 and 12p13 [8-9]. Fang et al reported a p53 gene mutation with loss of the normal allele from the secondary malignant fibrous histiocytoma developing in the background of fibrous dysplasia [10]. Since no p53 gene mutation has been detected in fibrous dysplasia, this may have occurred during progression from fibrous dysplasia to malignant fibrous histiocytoma, or thereafter. Thus, identification of the genes responsible for fibrous dysplasia and secondary sarcomas has become a current focus of interest.

References

1. Halawa M, Aziz AA: Chondrosarcoma in fibrous dysplasia of the pelvis. A case report and review of the literature. J

Bone Joint Surg British volume1984; 66: 760-4.
2. Ohmori K, Matsui H, Kanamori M *et al.* Malignant fibrous histiocytoma secondary to fibrous dysplasia. A case report. Int Orthop 1996; 20: 385-8.
3. Yabut SM Jr, Kenan S, Sissons HA *et al.* Malignant tranformation of fibrous dysplasia. A case report and review of the literature. Clin Orthop and Related Res 1988; 228: 281-9.
4. Coley BL, Stewart FW: Bone sarcoma in polyostotic fibrous dysplasia. Ann Surg 1945; 121: 872-81.
5. Ruggieri P, Sim FH, Bond JR *et al.* Malignancies in fibrous dysplasia. Cancer 1994; 73: 1411-24.
6. Schwartz DT, Alpert M: The malignant transformation of fibrous dysplasia. Am J Med Sci 1964; 247: 1420.
7. Bridge JA, Rosenthal H, Sanger WG *et al.* Desmoplastic fibroma arising in fibrous dysplasia. Chromosomal analysis and review of the literature. Clin Orthop and Related Res 1989; 247: 272-8.
8. Dal Cin P, Bertoni F, Bacchini P *et al.* Fibrous dysplasia and the short arm of chromosome 12. Histopathology 1999; 34: 279-80.
9. Dal Cin P, Sciot R, Brys P *et al.* Recurrent chromosome aberrations in fibrous dysplasia of the bone: a report of the CHAMP study group. CHromosomes And MorPhology. Cancer Genet Cytogenet 2000; 122: 30-2.
10. Fang Z, Mukai H, Nomura K *et al.* Establishment and characterization of a cell line from a malignant fibrous histiocytoma of bone developing in a patient with multiple fibrous dysplasia. J Cancer Res Clin Oncol 2002; 128: 45-9.
11. Campanacci M, Bertoni F, Capanna R: Malignant degeneration in fibrous dysplasia presentation of 6 cases and review of the literature. Ital J Orthop & Traumatol 1979; 5: 373-81.

肋骨之纖維化結構不良合併惡性變化—病例報告

簡迺娟 吳振都* 李元麒

骨骼之纖維化結構不良 (fibrous dysplasia) 被認為是一種發育異常，而非腫瘤。從纖維化結構不良之處產生惡性變化的機率很低，統計起來小於百分之一。我們報告一位 39 歲男性意外發現左側第二肋骨有一骨腫瘤，經手術切除後，病理檢查為骨骼之纖維化結構不良合併局部之惡性骨癌變化。術後在他院追加 5000 cGy 的電療。術後經兩年的追蹤並沒有發現復發或轉移。*(胸腔醫學 2004; 19: 152-156)*

關鍵詞：纖維化結構不良，惡性骨癌

國立台灣大學附設醫院 外科部 胸腔外科 病理部 *
索取抽印本請聯絡：簡迺娟醫師，國立台灣大學附設醫院外科部，台北市中山南路七號

Multiple Sclerosing Hemangiomas of the Lung with Lymph Node Metastasis — A Case Report

Chi-Hung Chen, Chi-Li Chung, Chi-Lang Fang*, Robert F. Chen**

Sclerosing hemangioma of the lung is an uncommon benign tumor of uncertain histogenesis. It is usually solitary and clinically benign with no instances of recurrence after excision. We report the case of a 40-year-old man with multiple sclerosing hemangiomas in the left lower lung accompanied by lymph node metastasis. These features suggested a very low-grade malignancy with metastatic potential. Tumor cells from the lungs and lymph node were focally immunoreactive for progesterone receptors, of which the clinical significance remains to be solved. The patient's postoperative course was good, and there was no evidence of recurrence 20 months after surgery.
(Thorac Med 2004; 19: 157-161)

Key words: sclerosing hemangioma, multiplicity, lymph node metastasis, progesterone receptor

Introduction

Sclerosing hemangioma of the lung is an uncommon benign tumor of the pulmonary parenchyma found predominantly in middle-aged women. The histology of the tumor was described in detail in the original paper of Liebow and Hubbell [1]. Microscopically, the appearance of the tumor varies and has four characteristic histologic patterns: solid, hemorrhagic, papillary, and sclerotic in different portions [2-3]. It is usually solitary and often presents as an asymptomatic coin lesion in the lower lung field, and is discovered incidentally by chest roentgenogram examination [2-4]. The tumor is clinically benign and surgically curable with no instances of recurrence after excision [2-4].

We report the case of a 40-year-old man with multiple sclerosing hemangiomas of the lung and lymph node metastasis. Progesterone receptors were detected on the tumor cells.

Case Report

A 40-year-old man was admitted to our hospital in 1999 for the evaluation of asymptomatic lung tumors that had been noted in a routine chest roentgenogram examination 2 weeks before. He had no history of chest pain, dyspnea, hemoptysis or cough. The chest roentgenogram showed two abnormal round lesions in the left lower lung field. (Figure 1)

On admission, a complete physical examination, laboratory examination, and panendoscopy revealed no abnormalities. Bronchoscopy was performed and showed negative findings. Since the possibility of a malignant neoplasm could not be excluded, he underwent a left lower lobectomy with dissection of the hilar and inferior pulmonary

Department of Chest Medicine, Taipei Medical University Hospital, Taipei; *Department of Pathology, Taipei Medical University, Taipei; **Department of Cardiothoracic Surgery, Taipei Medical University Hospital, Taipei
Address reprint requests to: Dr. Chi-Li Chung, Department of Chest Medicine, Taipei Medical University Hospital, 252 Wu-Hsing Street, Taipei, Taiwan

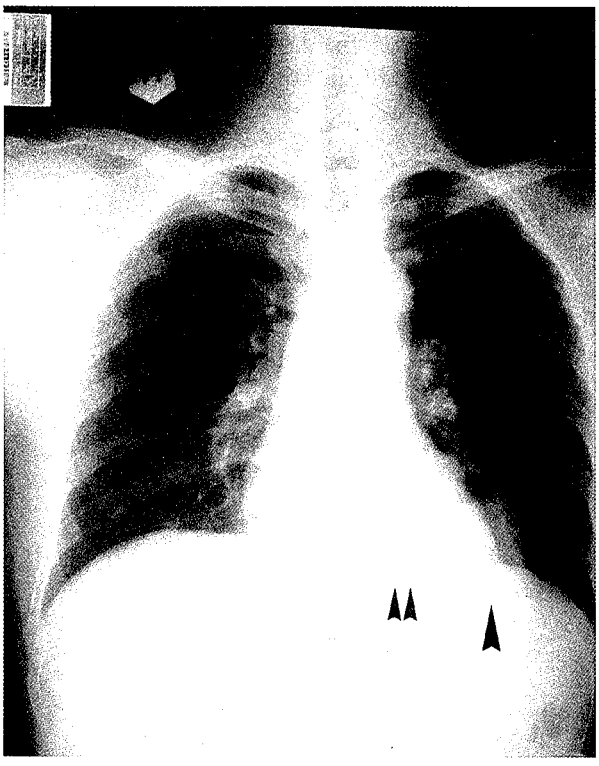

Fig. 1. Chest X-ray, PA view, preoperative film shows two nodular densities in the lower lung. (Double arrow, large tumor, 2.5 x 3 cm in size; single arrow, small tumor, 1.2 x 1cm in size)

ligament lymph nodes in July 1999.

Grossly, there were two indurated, confluent tumor masses measuring 6.2 x 5.5 x 3.5 cm^3 and 3 x 2 x 1.5 cm^3 in size, respectively, located at the left lower lobe. Foci of hemorrhage and calcification were also noted.

Histologically, the tumors were characterized by a mixture of solid, sclerotic, papillary, and hemorrhagic patterns, which was predominantly mixed solid and papillary patterns (Figure 2). The tumor cells were composed of polygonal cells with round to oval nuclei, fine chromatin, inconspicuous nucleoli, and abundant eosinophilic cytoplasmas. Marked calcification was also noticed in the sclerotic areas. In the papillary areas, type II pneumocyte-like cells lining the sclerosing core or solid nests were seen. One hilar node and one inferior pulmonary ligament node that were dissected out were involved in the sclerosing hemangioma (Figure 3). Immunohistochemically, the tumor cells revealed

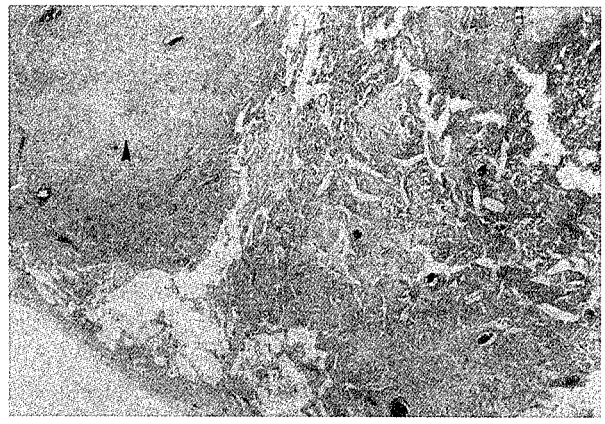

Fig. 2. The tumor with the picture of a sclerosing hemangioma growing in a solid (arrow, left upper) and papillary (right) pattern. (Hematoxylin & Eosin, original magnification x 40)

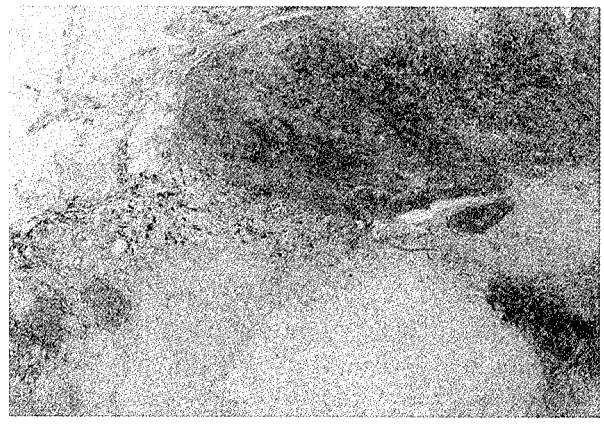

Fig. 3. A hilar lymph node was found to be involved in the sclerosing hemangioma. The lymph node tissue can be seen in the top third of the field and the tumor tissue in the lower two-thirds. (Hematoxylin & Eosin, original magnification x 40)

positive staining for vimentin, cytokerotatin and epithelial membrane antigen (EMA). Focally positive nuclear staining for progesterone receptors and negative for estrogen receptors was found in these tumor cells.

The postoperative course was uneventful and the patient remained in a stable condition with no recurrence noted at the 20 months' follow-up.

Discussion

Sclerosing hemangioma of the lung, an entity first described by Liebow and Hubbell in 1956, is

an uncommon lung tumor found predominantly in middle-aged women [1]. Most patients are discovered incidentally by chest radiography, in which a coin lesion in the lower lung field is often noted. However, other patients might complain of chest pain or hemoptysis [2-4]. These lesions often grow so slowly that no change in size on serial chest radiographs is noted during the observation periods. Most tumors have been cured by wedge resection or lobectomy, with no recurrence or distant metastasis being reported [2-4].

We experienced an asymptomatic man with a large pulmonary sclerosing hemangioma accompanied by a smaller mass with a histology identical to the main mass and in the same pulmonary lobe. Lymph node metastasis, including the left inferior pulmonary ligament and left hilar nodes, was also noted. The presence of progesterone receptors was detected on the resected specimen.

The histology of the sclerosing hemangioma had four characteristic patterns. Although the histological appearance was distinct and well defined, the histogenesis of the pulmonary sclerosing hemangioma was controversial. Liebow and Hubbell suggested this tumor was an endothelial proliferation, but another study favored mesothelial derivation [1,15]. However, based on immunohistochemical analysis, cells of sclerosing hemangiomas show positive staining for epithelial membrane antigen and surfactant apoprotein, and negative staining for factor VIII antigens for endothelial cells, suggesting that sclerosing hemangiomas might be derived from type II pneumocytes [3,17-19]. In spite of these studies, the exact nature and histogenesis remains uncertain. Recently, Devouassoux-Shisheboran and colleagues reported that sclerosing hemangiomas are derived from the primitive respiratory epithelium [13].

Sclerosing hemangiomas of the lung are generally considered to be single. Multiplicity is quite rare, usually with one dominant mass and smaller lesions nearby [2,5-7]. The case described by Noguchi had two larger lesions, up to 3.7 cm, and "innumerable' smaller ones in the right-lower lobe [6]. A rare incidence of bilaterality was described in the case reported by Lee et al., which had four masses separately distributed in the left lingular segment, left lower lobe, right middle lobe, and right lower lobe [7]. The case presented here showed a main tumor accompanied by a smaller one in the same lobe. The multiple lesions in the same lobe were considered to be transbronchial metastasis or multicentric origins of the tumor cells [5]. All these reported cases had an excellent prognosis after enucleation of the tumors.

Although the clinical course of sclerosing hemangiomas is usually benign, lymph node metastasis has been reported [9-10]. The phenomenon is extremely rare; two cases have been reported in the English-language literature [9-10]. The case described by Tanaka et al. had one solitary mass in the right lower lobe with a microscopic focus of hilar lymph node metastasis that consisted of cuboidal epithelial cells of the type II pneumocyte type, which was identical to the main component cells of the tumor in the lung [10]. This finding supports the neoplastic nature of pulmonary sclerosing hemangiomas. Due to the rarity of reported cases, it is uncertain whether the presence of a tumor spread to the regional lymph nodes carries a sinister prognosis. To date, there has been no evidence of spread outside the involved lymph nodes or of recurrence after excision in the reported patients, including the case presented here. Moreover, our case showed both multiple lung masses and lymph node metastasis at same time.

More than 80 percent of cases of pulmonary sclerosing hemangioma have occurred in women, especially during their reproductive age [1-3]. One possibility is the presence of steroid receptors on the gender-specific tumor, and that the tumor growth is responsive to physiological hormonal alteration [12]. Few studies have tried to investigate the reason for the female preponderance. Aihara and Nakajima reported the quantitative analysis of estrogen and progesterone receptors by enzyme immunoassay in eight cases, which showed estrogen receptors (ER) present in seven cases, and progesterone receptors (PR) in all cases [11]. However, the four female cases reported by Ohori et al. revealed negative

immunohistochemical results [12]. Our case showed positive PRs in the cuboidal epithelial cells of the tumor, but ER was absent. The difference between those cases previously reported and the present one is that the former all had a solitary lesion and lacked lymph node metastasis. However, the significance of the status of the estrogen and progesterone receptors on pulmonary sclerosing hemangiomas is still uncertain. The reasons are that too few cases have undergone an analysis of their receptor status, and receptors did not exist on all the examined tumors. In addition, hormonal therapy had never been tried due to the benign postoperative course. Further studies will be necessary for a full understanding of the steroid hormone receptor status and its association with the biological behavior of pulmonary sclerosing hemangiomas.

In conclusion, this report is unique in that it describes very rare manifestations of pulmonary sclerosing hemangioma including multiplicity and lymph node metastasis that were simultaneously found in a male patient. These features of the present case may suggest a low-grade malignancy with the capacity for intrapulmonary spreads and metastasis. The role of the presence of progesterone receptors on the tumor cells remains to be clarified.

References

1. Liebow AA., Hubell DS: Sclerosing hemangioma (histiocytoma, xanthoma) of the lung. Cancer 1956; 9: 53-75.
2. Katzenstein AA, Gmelich JT, Carrington CB: Sclerosing hemangima of the lung: a clinicopathologic study of 51 cases. Am J Surg Pathol 1980; 4: 343-56.
3. Chan KW, Gibbs AR, Lo WS, Newman GR: Benign sclerosing pneumocytoma of the lung (sclerosing hemangioma). Thorax 1982; 37: 404-12.
4. Sugio K, Yokoyama H, Kanedo S, Ishida T, Sugimachi K: Sclerosing hemangioma of the lung: Radiographic and pathological study. Ann Thorac Surg 1992; 53: 295-300.
5. Joshi K, Shankar SK, Gopinath N: Multiple sclerosing hemangiomas of the lung. Postgrad Med J 1980; 56: 50-3.
6. Noguchi M, Kodama T, Mornaga S, *et al.* Multiple sclerosing hemangiomas of the lung. Am J Surg Pathol 1986; 10: 429-35.
7. Lee ST, Lee YC, Hsu CY, Lin CC: Bilateral multiple sclerosing hemangiomas of the lung. Chest 1992; 101: 572-3.
8. Shimosato Y: Lung tumors of uncertain histogenesis. Sem in Diag Pathol 1995; 12: 185-92.
9. Spencer H, Nambus S: Sclerosing hemangioma of the lung. Histopathology 1986; 10: 477-87.
10. Tanaka I, Inoue M, Matsui Y, *et al.* A case of pneumocytoma (so-called sclerosing hemangioma) with lymph node metastasis. Jpn J Clin Oncol 1986; 16: 77-86.
11. Aihara T, Nakajima T: Sclerosing hemangioma of the lung: Pathological study and enzyme immunoassay for estrogen and progesterone receptors. Acta Pathol Jpn 43: 507-15.
12. Ohori NP, Yousem SA, Sonmez-Alpan E, *et al.* Estrogen and progesterone receptors in lymphangioleiomyomatosis, epitheloid hemangioendothelioma, and sclerosing hemangioma. Am J Clin Pathol 1991: 96: 529-35.
13. Devouassoux-Shisheboran M, Hayashi T, Linnoila RI, *et al.* A clinicopathologic study of 100 cases of pulmonary sclerosing hemangioma with immunohistochemical studies. Am J Surg Pathol 2000; 24: 906-16.
14. Katzenstein A-LA, Fulling K, Weise DL, Battifora H: So-called sclerosing hemangioma of the lung: evidence for mesothelial origin. Am J Surg Pathol 1983; 7: 3-14.
15. Hill GS, Eggleston JC: Electron microscopic study of so-called "pulmonary sclerosing hemangioma". Report of a case suggesting epithelial origin. Cancer 1972; 30: 1092-106.
16. Haimoto H, Tsutsumi Y, Nagura H, *et al.* Immunohistochemical study of so-called sclerosing hemangioma of the lung. Virchows Arch (Pathol Anat) 1985; 407: 419-30.
17. Yousem SA, Wick MR, Singh G, *et al.* So-called sclerosing hemangiomas of the lung: An immunohistochemical study supporting a respiratory epithelial origin. Am J Surg Pathol 1988; 12: 582-90.
18. Nagata N, Dairaku M, Ishida T, *et al.* Sclerosing hemangioma of the lung: Immunohistochemical characterization of its origin as related to surfactant apoprotein. Cancer 1985; 55: 116-23.

肺臟多發性血管瘤合併淋巴結轉移—病例報告

陳基宏　鍾啟禮　方嘉郎*　陳復銓**

肺臟性血管瘤是一種不常見的良性腫瘤，好發於30至40歲的中年女性。臨床上無症狀較多，大部份的病患都是在例行性的胸部X光片檢查之後才意外的發現。通常是銅幣狀的單一病灶且多位於下肺部。肺臟性血管瘤生長速度很慢而且在外科完全切除之後沒有復發的報告病例。本篇報告一位40歲的男性在例行性的X光片檢查之後發現兩個銅幣狀的病灶，在開刀後病理報告發現有淋巴轉移。病患在術後狀況良好，經門診追蹤20個月並無復發的現象。*(胸腔醫學 2004; 19: 157-161)*

關鍵詞：血管瘤，多發性，淋巴轉移

台北醫學大學附設醫院　胸腔內科　病理科*　心臟血管暨胸腔外科**
索取抽印本請聯絡：鍾啟禮醫師，台北醫學大學附設醫院胸腔內科，台北市吳興街252號

Pulmonary Tumor Embolism as an Initial Manifestation of Cervical Cancer — A Case Report

Yun-Sung Chen, Hao-Chien Wang, Yih-Leong Chang*, Pan-Chyr Yang**

Pulmonary tumor embolism is rarely the initial manifestation of cervical cancer. It is difficult to obtain a definite diagnosis because there are neither specific clinical presentations nor non-invasive diagnostic tests. A poor prognosis is expected because of the delay in diagnosis and the consequent irreversible cardiopulmonary alterations. However, a high index of suspicion may help in the early diagnosis of this disease. Herein, we present a 58-year-old female patient with cervical cancer that initially manifested as pulmonary tumor embolism. The subacute onset of symptoms related to cor pulmonale with rapid deterioration and mortality because of massive tumor embolism are noted in the case. Radiographic studies and pathological findings are demonstrated as well. ***(Thorac Med 2004; 19: 162-167)***

Key words: pulmonary tumor embolism, cervical cancer, squamous cell carcinoma

Introduction

Tumor embolism is considered a rare cause of pulmonary embolism and is infrequently diagnosed. Even in patients with malignancy, the occurrence of pulmonary embolism is usually attributed to hypercoagulable states rather than tumor microemboli. However, a significant proportion of underdiagnoses or misdiagnoses of pulmonary tumor embolism have been found at autopsy [1]. Since the treatment and prognosis of tumor embolism is quite different from that of thrombotic pulmonary embolism, it is necessary to be familiar with the clinical presentations of and diagnostic tests for pulmonary tumor embolism to achieve an early diagnosis. We present herein a case of pulmonary tumor embolism as an initial manifestation of cervical cancer, and briefly review the related literature.

Case Report

A 58-year-old woman was admitted in January 2002 because of progressive dyspnea and dry cough for 2 weeks. No associated symptoms, such as orthopnea, paroxysmal nocturnal dyspnea, fever, chest pain, or hemoptysis, were noted. There was no history of any major systemic disease. The menstrual cycle had been regular, but had already ceased for years. Her physical examination revealed fine crackles in both lower lungs, without cardiac murmur, bipedal edema, or lymphadenopathy. Arterial blood gas measurements showed a pH of 7.436, PCO_2 of 33.5 mmHg, and PO_2 of 60.7 mmHg in room air. Anemia (hemoglobin: 10.2 g/dl) and hypoalbuminemia (serum albumin: 2.92 g/dl) were

Department of Internal Medicine Far Eastern Memorial Hospital, Taipei County, Taiwan, The Department of Pathology* and Internal Medicine** National Taiwan University Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Hao-Chien Wang, Department of Internal Medicine Far Eastern Memorial Hospital, No. 21, Section 2, Nanya South Road, Taipei County, Taiwan 220

also noted. The plasma D-dimer level was 3.46 μg/ml, fibrin degradation products concentration was 20-40 μg/ml, and the 3P test was positive.

Other laboratory investigations were unremarkable. The electrocardiograph was normal. The chest radiograph showed increased infiltrations in the lower lung fields (Figure 1). Computed tomography demonstrated subpleural consolidation and dilated peripheral pulmonary arteries in the right lower lung (Figure 2). Pulmonary function tests disclosed a moderately restrictive ventilatory defect with severe impairment of diffusion capacity. A ventilation-perfusion lung scan revealed diffuse multiple non-segmental small defects in both lungs (Figure 3). Ultrasonography of the lower extremities revealed no evidence of deep venous thrombosis. A transthoracic echocardiogram disclosed a dilatation of the right atrium and ventricle with moderate tricuspid regurgitation and pulmonary hypertension.

The patient was treated with heparin due to the suspicion of pulmonary embolism. However, the symptoms did not improve. She then underwent a video-assisted thoracoscopic lung biopsy. The specimens showed clusters of tumor emboli within pulmonary arterioles in the interstitium and the subpleural area diffusely (Figure 4). The morphology of the tumor cells was compatible with a metastatic squamous cell carcinoma (Figure 5). Papanicolaou smear and curretage of the cervix both revealed squamous cell carcinoma. Chemotherapy for stage IV cervical squamous cell carcinoma was then arranged. Unfortunately, her condition suddenly deteriorated before the scheduled chemotherapy. Refractory hypoxemia and circulatory collapse

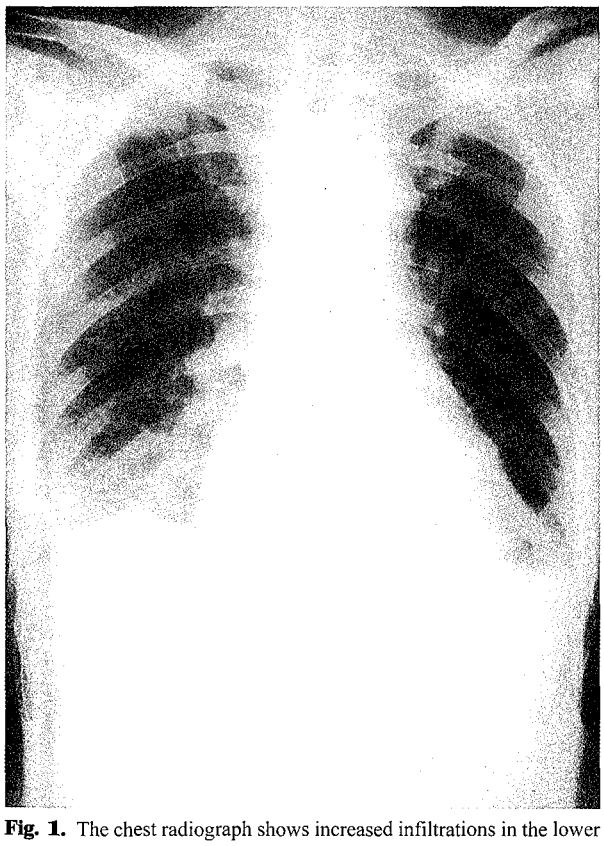

Fig. 1. The chest radiograph shows increased infiltrations in the lower lung fields.

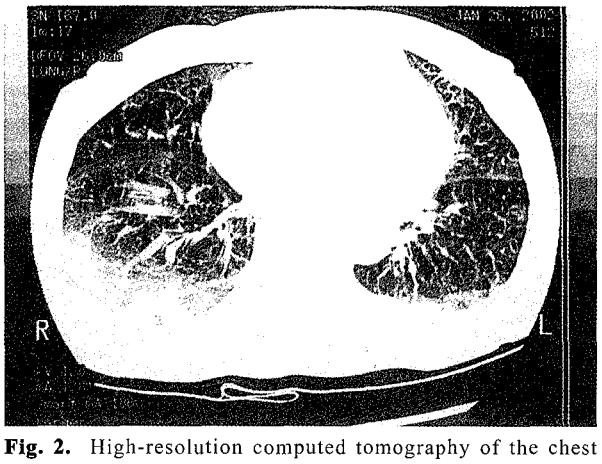

Fig. 2. High-resolution computed tomography of the chest demonstrates subpleural consolidation and dilated peripheral pulmonary arteries in the right lower lung.

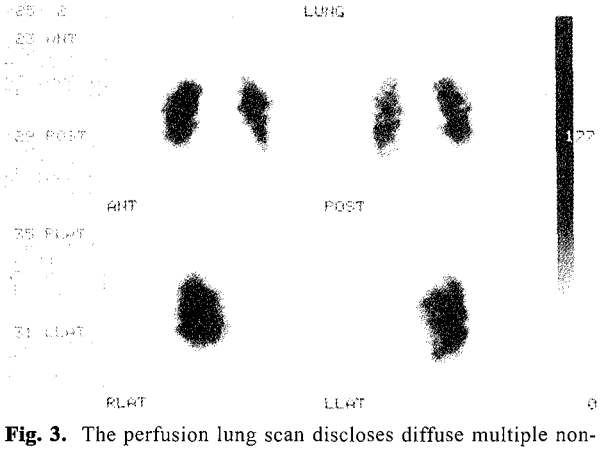

Fig. 3. The perfusion lung scan discloses diffuse multiple non-segmental small defects in both lungs.

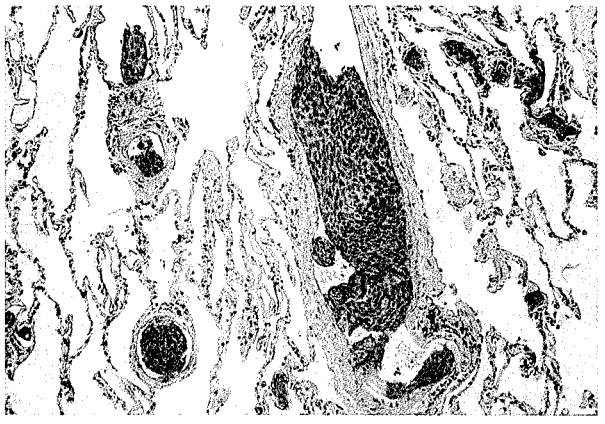

Fig. 4. Disseminated tumor emboli are noted in the pulmonary interstitium. The tumor cells are compatible with a metastatic squamous cell carcinoma. (Hematoxylin and eosin, X33 original magnification)

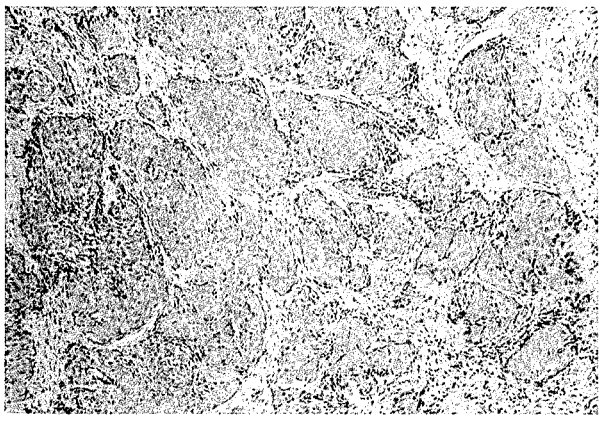

Fig. 5. The cervical biopsy reveals a primary squamous cell carcinoma. (Hematoxylin and eosin, X33 original magnification)

ensued rapidly. Massive pulmonary embolism was likely. She passed away 6 weeks after admission.

Discussion

The incidence of pulmonary tumor embolism among patients with carcinoma varies widely, from 0.9% to 26% in autopsy series, depending on the primary site of malignancy. It is considered to be the cause of death in 1% to 8% of diagnosed cases. The most frequently reported cases involve carcinoma of the breast, lung, liver, stomach, kidney, and choriocarcinoma [2-5]. In addition, a variety of malignancies are implicated as sources of pulmonary embolism in many isolated case reports [6]. Histologically, adenocarcinoma is seen in 90% of these reported cases [7].

The clinical manifestations of pulmonary tumor embolism are quite similar to those of thromboembolic pulmonary disease. The only difference may be the development of further emboli during anticoagulation. Presenting symptoms, signs, and laboratory data in one report did not reveal any differences between the two groups, except a higher incidence of cough among the patients with tumor embolism [1].

There is no clinical presentation specific to pulmonary tumor embolism. The most common presentation is subacute progressive dyspnea, ranging from a few days to 6 months in duration. Physical examination usually demonstrates signs of pulmonary hypertension in association with tachycardia and tachypnea [8]. Hypoxemia and respiratory alkalosis are nearly always present. The electrocardiograph and echocardiograph may show findings compatible with cor pulmonale, but none is specific to tumor embolism [9]. The chest radiograph is often unremarkable, while pulmonary infarction or diffuse infiltrates are occasionally noticed [3].

For the definitive diagnosis of pulmonary tumor embolism, open lung or trans-bronchial lung biopsy remains the procedure of choice. Pulmonary wedge aspiration cytology may also confirm the presence of malignancy in the pulmonary arterial bed [10]. Other less invasive tests, such as ventilation-perfusion lung scan, computed tomography, and pulmonary angiography, may also be helpful in establishing the diagnosis.

The most commonly described pattern of ventilation-perfusion lung scan is that of multiple, small, peripheral, or sub-segmental perfusion defects with normal ventilation. Other perfusion patterns seen with tumor emboli include normal scans, focal segmental defects, or complete lung defects. In such cases, differentiating a tumor from a pulmonary embolism is extremely difficult [11].

The findings of dilated and beaded peripheral pulmonary arteries in computed tomographic scans,

primarily in a sub-segmental distribution involving multiple lobes, are highly suggestive of metastatic intravascular tumor emboli. Beaded vessels are attributed to a distension of the medium and small pulmonary arteries by tumor emboli [12]. Peripheral wedge-shaped opacities distal to some abnormal pulmonary arteries suggest pulmonary infarcts [13].

The pulmonary angiography is most often normal. A distinct thrombus is not usually seen. If a distinct thrombus is visualized, an alternative diagnosis of venous thromboembolic disease should be considered [14].

Although pulmonary tumor embolism and lymphangitis carcinomatosis are clinically similar diseases, they are morphologically different entities. Right ventricular hypertrophy-dilatation, histological signs of pulmonary hypertension, and hemorrhagic infarcts are more prevalent in the cases with tumor embolism. Respiratory distress as the main cause of death is significantly more frequent in cases with tumor embolism [15].

Pulmonary tumor embolism may develop at any time in neoplastic patients, but is rarely the initial sign of the disease [16]. It is also a very unusual finding in patients with cervical cancer [17]. A correct diagnosis is often difficult and is based on a high index of suspicion. This implies a worse prognosis than parenchymal metastases or lymphangitis because of the irreversible cardiopulmonary alterations [18]. Some case reports have suggested favorable results with chemotherapy or surgical resection of tumor emboli. Nevertheless, little information is available about the results of these therapies in cervical cancer patients.

In conclusion, although a pulmonary tumor embolism is rarely the initial manifestation of neoplasm, it should be considered in the differential diagnosis of subacute progressive dyspnea in patients at risk of malignancy. Early diagnosis may help in avoiding unnecessary anticoagulation and improving the patient's prognosis.

References

1. Goldhaber SZ, Dricker E, Buring JE, *et al.* Clinical suspicion of autopsy-proven thrombotic and tumor pulmonary embolism in cancer patients. Am Heart J 1987; 114: 1432-5.
2. Kane RD, Hawkins HK, Miller JA, *et al.* Microscopic pulmonary tumor emboli associated with dyspnea. Cancer 1975; 36: 1473-82.
3. Winterbauer RH, Elfenbein IB, Ball WC Jr. Incidence and clinical significance of tumor embolization to the lungs. Am J Med 1968; 45: 271-90.
4. Veinot JP, Ford SE, Price RG. Subacute cor pulmonale due to tumor embolization. Arch Pathol Lab Med 1992; 116: 131-4.
5. Tamura A, Matsubara O. Pulmonary tumor embolism: relationship between clinical manifestations and pathologic findings. Nihon Kyobu Shikkan Gakkai Zasshi 1993; 31: 1269-78. [In Japanese English abstract]
6. Bassiri AG, Haghighi B, Doyle RL, *et al.* Pulmonary tumor embolism. Am J Respir Crit Care Med 1997; 155: 2089-95.
7. von Herbay A, Illes A, Waldherr R, *et al.* Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. Cancer 1990; 66: 587-92.
8. Schriner RW, Ryu JH, Edwards WD. Microscopic pulmonary tumor embolism causing subacute cor pulmonale: a difficult antemortem diagnosis. Mayo Clin Proc 1991; 66: 143-8
9. Soares FA, Landell GA, de Oliveira JA. Pulmonary tumor embolism to alveolar septal capillaries. An unusual cause of sudden cor pulmonale. Arch Pathol Lab Med 1992; 116: 187-8.
10. Bhuvaneswaran JS, Venkitachalam CG, Sandhyamani S. Pulmonary wedge aspiration cytology in the diagnosis of recurrent tumour embolism causing pulmonary arterial hypertension. Int J Cardiol 1993; 39: 209-12.
11. Boudreau RJ, Lisbona R, Sheldon H. Ventilation-perfusion mismatch in tumor embolism. Clin Nucl Med 1982; 7: 320-2.
12. Shepard JA, Moore EH, Templeton PA, *et al.* Pulmonary intravascular tumor emboli: dilated and beaded peripheral pulmonary arteries at CT. Radiology 1993; 187: 797-801.
13. Chan CK, Hutcheon MA, Hyland RH, *et al.* Pulmonary tumor embolism: a critical review of clinical, imaging, and hemodynamic features. J Thorac Imaging 1987; 2: 4-14.
14. Shapiro JM, Avigan DE, Warshofsky MK, *et al.* Acute cor pulmonale due to tumor emboli. Diagnosis by pulmonary

artery catheterization. N Y State J Med 1993; 93: 197-8.
15. Soares FA, Pinto AP, Landell GA. Pulmonary tumor embolism to arterial vessels and carcinomatous lymphangitis. A comparative clinicopathological study. Arch Pathol Lab Med 1993; 117: 827-31.
16. Montero A, Vidaller A, Mitjavila F, *et al.* Microscopic pulmonary tumoral embolism and subacute cor pulmonale as the first clinical signs of cancer. Acta Oncol 1999; 38: 1116-8.
17. Varma JS. Subacute pulmonary hypertension and systemic tumour embolism from cervical cancer. Scott Med J 1982; 27: 336-40.
18. Soares FA, Landell GA, de Oliveira JA. Clinical aspects of tumour involvement of the pulmonary vessels. Acta Oncol 1992; 31: 519-23.

以肺腫瘤栓塞爲初始表現之子宮頸癌—病例報告

陳運嵩　王鶴健　張逸良*　楊泮池**

以肺腫瘤栓塞為初始表現的子宮頸癌非常罕見。由於缺乏特定的臨床表現，又沒有非侵襲性的檢查可以確定診斷，使此種疾病的診斷更加困難。診斷上的延遲及不可逆的心肺病變，為其預後不佳的主因。因此，保持高度的警覺，將有助於疾病的早期診斷。我們報告一位五十八歲的子宮頸癌病患，以肺腫瘤栓塞為癌症的初始表現。其早期的臨床表現以亞急性肺心症之症狀為主，最後則因為大量的腫瘤栓塞造成病情急速惡化而死亡。其放射學檢查及病理切片結果亦呈現典型的肺腫瘤栓塞變化。***(胸腔醫學 2004; 19: 162-167)***

關鍵詞：肺腫瘤栓塞，子宮頸癌，鱗狀細胞癌

財團法人亞東紀念醫院　內科部，國立台灣大學附設醫院　病理部*　內科部**
索取抽印本請聯絡：王鶴健醫師，財團法人亞東紀念醫院內科部，台北縣板橋市南雅南路二段 21 號